(5)

Pathology مقرر المتفوق

microbiology انواع الـ

Q/ nail psoriasis
Q/ Koebner ---
Q/ psoriatic Arthritis
Q/ Pustular Ps.
no → Pregnancy

methotrexate / cyclosporine

Psoriasis

Def.: Common, chronic, idiopathic inflammatory skin disorder with unpredictable remission and relapse. (Serious & Systemic)

Epidemiology:

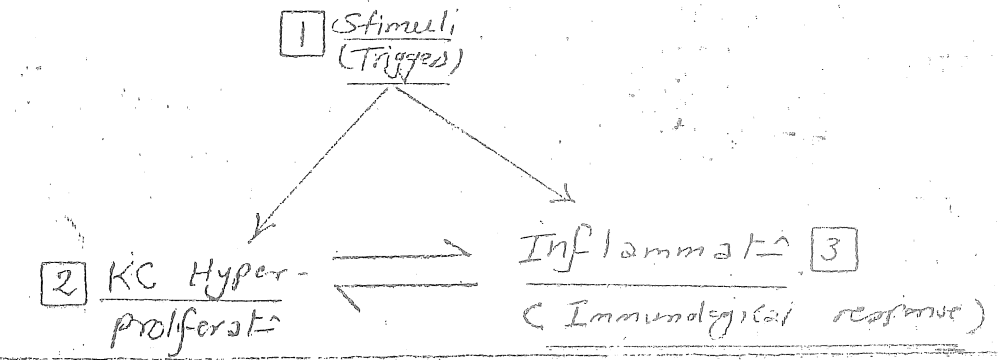
Incidence: 1-2% of general populations.

Age: any, but commenest between (15-40 Ys). (mean 33 y).

Sex: no predilection.

Pathogenesis of psoriasis
(Hunter's dermatology 2008)

The Exact Etiopathogenesis is unknown but there are 3 key features (Triad) w interacts with each others.



مناقشة كل عامل بالتفصيل

A. Triggers (Stimuli) of PS.:

1. **Genetics:**
   - There are 2 Types of PS Acc. to the Inheritance Mode (see the table).

Inheritance is polygenic & Genetic loci are:

- Psor S1 (Chromosome 6).
- Psor S2 (" 17).

- Ttncid of HLA < B13 & Cw6 (Early onset Ps.)
  B27 (Pustular Ps & Ps. arthropathy).

- FH in ps. Ch- By:
  - +ve in 30% of cases.
  - if 1 parent affected ⟶ 16% Chance of offspring Affection.
  - if 2 parents affected ⟶ Chance of 50%.

If one of my parents has psoriasis, what's the chance that I'll get psoriasis?

والأب أخطر من الأم في التوريث (Genetic Imprinting)

- Twins affect-:
  - MonoZygotic (متماثل) → 73%.
  - DiZygotic (غير متماثل) → 20%.

- Types of PS:

	Type I (Commonest)	Type II (less common)
Onset	Early (20 Ys)	Late (50-60 Ys)
Course	More generalized & Severe	Mild & Localized
FH	Common	Rare
HLA	Cw6 (Frequently)	Rare

2. Trauma: → d.t Koebner phenomenon.
3. Infect-: → Staphylococci may act as a Superantigen
   usually: pharyngitis & ± dental inf.
   both may ⟶ Plt. of Pustular Ps., Exacerbate of plaque ps. & Flare of Guttate.
4. Stress: → release substance P ⟶ Neurogenic inflamm. (so Capsaicin may be used in HH).
5. Drugs: → Drug induced ps. lithium, BBs, Antimalarial, TKN
6. Climatic: → ps. improves ☀ Summer & Exacerbate in Winter. (Wbr).
7. Hormones:
   - Ps ↑↑ by: Puberty, Menopause & Hypocal
   - Ps ↓↓ by: pregnancy (±).

(8.) KC Hyperproliferation (↑↑ Epidermopoiesis)

(Epidermal Cell Kinetics in Psoriasis)

2 important Events

- ↑↑ growth Fraction. (GF)
  - ↑↑ Ns of germinative cells that enter the Cell Cycle (1oo: in Ps compared to 3o: of Basal KCs in NL skin).
- Shortened Epidermal renewal Time (Turnover).
  - in NL skin, it's 3o-6o d, while in Psoriatic skin it ↓↓ to ≤ 7-1o ds.

[إبقاء الخلايا القاعدية في الطبقة القاعدية]
[Corneocytes تكون ... إلخ]

Both → "out of control prolif. (Hyperprolif).

- Exceeds Capacity of desquamation → Scales.
- retent° of Nuclei → Parakeratosis

- Etiology & mechanism of Hyperprolif: unknown but ↓ d.t:

① ↑Hs Wound healing like process & Sc;
cGMP, NO-Synthase, Polyamines, Calmodulin all are ↑.

② Genetic defect in control of KC growth.
→ subNL activat° of Transcription Factors:
- STAT-1α (NLLy++ by IFN-γ)
- NFκB.

NB: Epidermopoiesis ↑ → Continuous rate of epid. prolif.
- Turnover = Transit time: زمن التجدد
- Growth Fraction: % of dividing Basal cells.
- ↑ Epidermopoiesis is d.t either ↑ Growth Fraction or shortened Transit time or Both.

C. Inflammation

(Immunological Response in Ps).

Triggers (Inf., Trauma, Stress).

↓

++ KCs

↓ Secrete.

IL1

IL8

NB. Also Attract Neut. to epid. → "Microabsess of Munro"

1. ↑↑ Expression of ICAM-1 & E Selectin on Vascular endothelium of papillary dermal BVs. →

Accumulation of T-lymphocytes (CLA +ve memory cells) & CD4 Their adhesion to Vascular Endoth. Through interaction of their LFA-1 with ICAM-1 & E Selectin on Vascular Endoth.

(ترتبط للصم الذين مع بعض بتحدد (ICAM)

2. تجمع T-cell في البابلا → Endothelium of papillary dermal BVs

هاكتاع تعدّى من فوق جدار الوعية الدموية الى داخل الـ Derm's وهذه العملية تسمى

"T-cell Trafficking"

IL8 → attract T-lymphocytes into Dermis where they (interact) with the:

APCs (LHCs).

↓

The interaction bet T-cells & APCs occurs through (3 signals) & ends by T cells (Activation & differentiation)

(C) Inflammation

(Immunological Response in ps).

Triggers (Inf. / Trauma / Stress).

↓

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↓

يؤدي للصاق الخلايا بعضها ببعض (ICAM)

2. يعيد تجمع T-cell الى الخارج → Endothelium of Papillary dermal BVs

فتتجمع مرة اخرى في الطبقة الحليمية Dermis's الى داخل الـ وهذه العملية تسمى

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٣ تفاعلات بيحصل بين (LCs) و (TC)

T Cells are Activated by LCs Through 3 sets of Signals

① 1st Signal (Ag recognition): recognition of Ag Bound To MHC-II (on LCs) by TCRs (on T Cells)

(Ag) بتعرف على

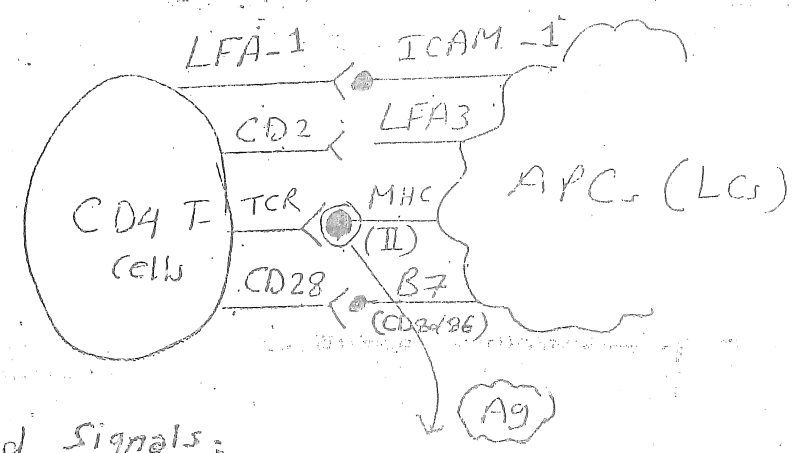
major histocompatibility complex

② Costimulatory Signals:

T Cells تنشيط ال

عن طريق مستقبلات LCs على

Coordinated stimulation of T Cells by Costimulatory molecules present on surface of APCs.

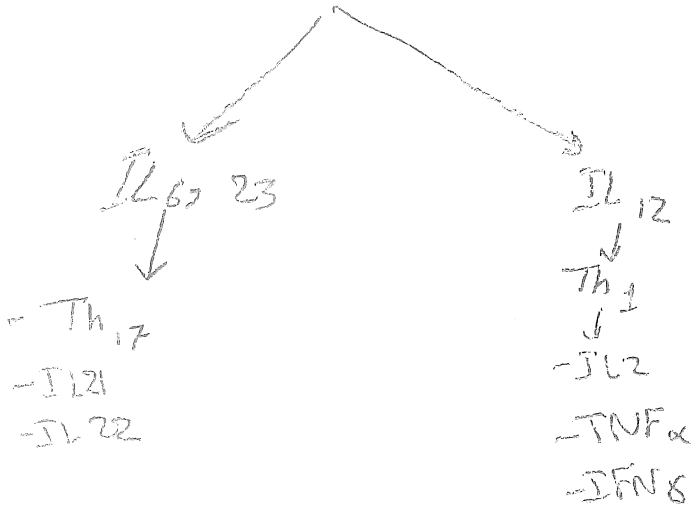


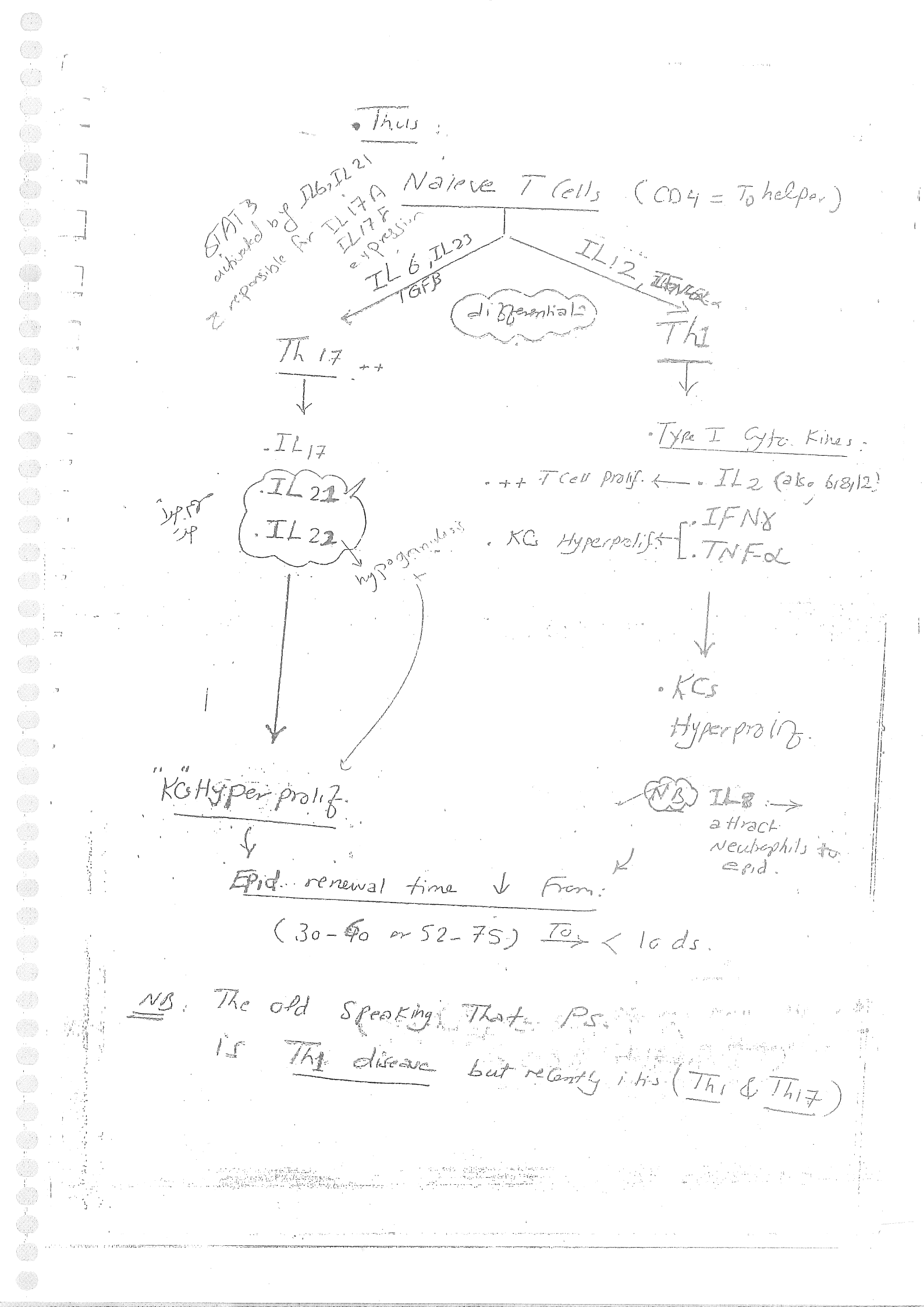
③ 3rd Signals:

↓

Cytokines release & Interaction with Their Receptors.

(Release of cytokines From APCs IL-6, IL-12 → CD4 differentiation)


IL 6, 23
IL 12
Th 17
- IL21
- IL 22
Th 1
- IL 2
- TNF α
- IFN δ


• Thus:
Naive T cells (CD4 = T0 helper)
STAT3 activated by IL6, IL21 responsible for IL17A IL17F expression
IL6, IL23
TGFβ
differentials
IL12, IL18
Th17 ++
Th1
IL17
IL21
IL22
hyperproliferation
Type I Cyto. Kines.
++ T cell prolif. ← IL2 (also, 6, 18, 12)
KC Hyperplasia
IFNγ
TNF-α
KCs Hyperprolif.
"KC Hyperprolif."
NB
IL8 → attract neutrophils to epid.
Epid. renewal time ↓ From:
(30-40 or 52-75) T0 → < 10 ds.
NB. The old Speaking That Ps. is Th1 disease but recently it's (Th1 & Th17)

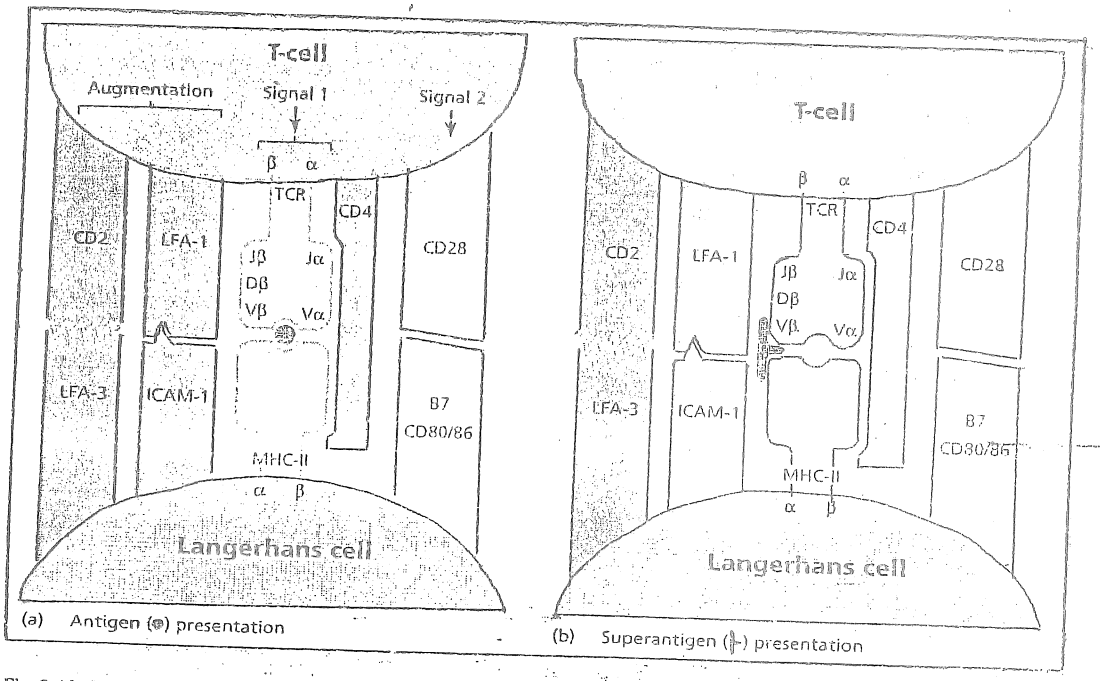


Fig. 2.12 T-lymphocyte activation by (a) antigen and (b) superantigen. When antigen has been processed it is presented on the surface of the Langerhans cell in association with major histocompatibility complex (MHC) Class II. The complex formation that takes place between the antigen, MHC Class II and T-cell receptor (TCR) provides signal 1, which is enhanced by the coupling of CD4 with the MHC molecule. A second signal for T-cell activation is provided by the interaction between the costimulatory molecules CD28 (T cell) and B7 (Langerhans cell). CD2/LFA-3 and LFA-1/ICAM-1 adhesion augment the response to signals 1 and 2. Superantigen interacts with the TCR Vβ and MHC Class II without processing, binding outside the normal antigen binding site. Activated T cells secrete many cytokines, including IL-1, IL-8 and interferon-γ, which promote inflammation (Fig. 2.13).

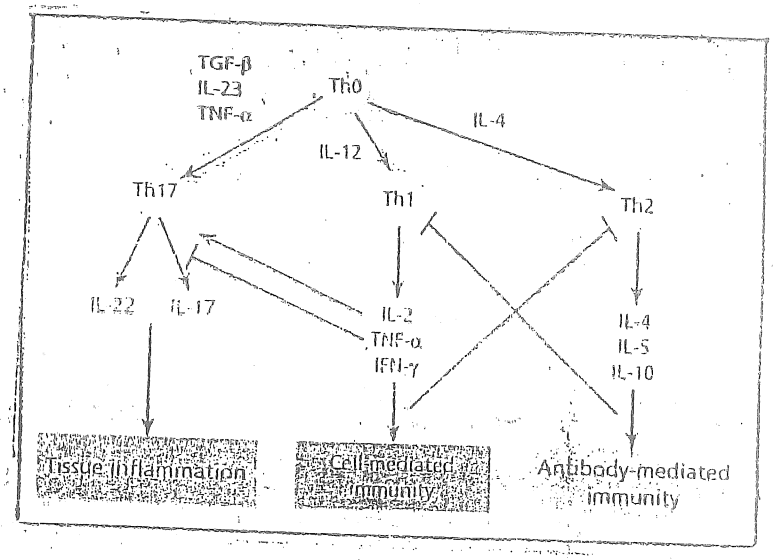


Fig. 2.13 Characteristics of Th1, Th2 and Th17 responses.

Clinical Picture of Psoriasis

- **Psoriasis may affect:**
  - Skin
  - MM
  - Hair
  - Nail
  - Joint
  - Eye (ocular psoriasis)

> • The Most Important systemic Association are:
> (1) Ps. Arthritis (2) Metabolic Synd.

(A) Psoriasis of Skin:

Classical Type

(Ps. vulgaris = plaque ps)

- **Subtypes (varieties):** according to shape 1-8, according to site A

1. Guttate
2. Annular
3. Linear
4. Nummular — most common form
5. Geographic
6. Ruporid
7. Flexural (inverse ps).
8. Pp (palmoplantar)
   - A. Scalp.
   - B. Nail ps
   - C. Sub. ps
   - D. Mucosal
   - E. Follicular
   - F. Elephantine
   - G. osteoarticular

Variants

- Drug induced
- Pustular ps.
- Erythrodermic ps.
- unstable ps. (phases in the dis. & unpredictable course & marked activity).

- **Ps. vulgaris = chr. plaque ps.: "Plaques Ch. By":**
  - well defined, raised, Erythematous, Asympt. or itchy, Covered & Silvery scales.
  - **Sites:** any site but commonest: Extensor limbs, Elbows, Knees, sacral & scalp.

- **Grattage test:** Scraping of psoriatic lesions with edge of glass slide → removal of scales layer after layer till a thin membran (Buckley's memb.) is reached → on its removal → Pin Point Hges occurs (Auspitz sign).

- What is Auspitz Sign & what its Cause:
  - it is a pin point Hgic spots induced by Gratlage test; representing the excoriations of the Thin Supra papillary portions & exposure of dilated Vs on tip of dermal papillae.
- Sub Types of Ps. Vulgaris:
  1. Guttate (water drops): Ch BY:
     - Abrupt onset.
     - Following Sheptococcal inf.
     - usually < 30 Yrs & Children.
     - Rx → of Ps. + Antibiotics or Tonsillectomy.
     - prognosis → good in children & chronic in adults.
  2. Annular: d.t Central involution of plaque or Coalescence of multiple papules.
  3. Nummular: Coin Shapped.
  4. Linear: d.t Koebner phenomenon.
  5. Geographic: Curved patterns.
  6. Rupoid: Heavily Crusted (simulating ∴ Rupia) "Ostraceous"
  7. Flexural (Inverse or Intertrigenous Ps.):
     - affect intertrigenous areas ??
     - Clp → well defined Erythema but usually NP ↓ Scaling (d.t Moisture) < Itching is marked.
  8. Palmoplantar: → many patterns
     - Silvery, Scaly patches + Erythema.
     - Fissured, thick plaques.
     - Pustular.
     - Rupoid: Crusted, Hard lamellar, Oyster shell like

differentiated from Ecz. by Sharp Margin at Wrist.

9. Scalp Psoriasis: → Several patterns:

ⓐ. diffuse (Erythema + Silvery scaling).

ⓑ. discrete discoid plaques

Corona ← ⓒ. Corona Psoriatica: "Ant. Hair line involvem."

ⓓ. Pityriasis Amiantacea.

ⓔ. seboPsoriasis.

NB: (1.) Pityriasis Amiantacea:

. descriptive term (not a dis.) denoting soft patches with firm adherent asbestose like scales (hair is matted).

. Etiology: ± 2ry bact. inf. occuring on top of:

. Eczema: AD or SD.

. Psoriasis or

. T. Capitis.

. Mx: ① Topical Keratolytics:

→ ② Shampooing e.g. Tar, S or Selenium

help separat. of crust & improve inf.

85 Case Studies:
- 35% → Ps
- 35% → Eczema
- 13% → T. capit.

Psoriasis is the most common cause

(2) SeboPsoriasis: Term applied to psoriatic lesions involving the scalp, eye brow, Ears

ⓐ have features of both diseases (Ps. or SD) or changin during the course between Ps. & SD.

(3) DD from SD:

Ps: dry silvery scales, Marginal involvement, Mild itching, ± Hair loss.

SD: greasy, large scales, diffuse involvem., Marked itching, No hair loss.

NB: PS. is more itchy in the following

Conditions: 1. Flexural PS.
2. Psychogenic disturbance
3. CD of Topicals.

(B) PS. of The MM.:

. MM is not involved in PS. Except in the Setting of pustular & Erythrodermic Types, varieties ±:

- Silvery Scaling at lips.
- Gray or White Plaques.
- Annular lesions.
- Geographic Tongue. ⟶ (Annulus Migrans).

• Geographic Tongue:

2 Varieties:

1. Circinate or annular raised white lines
2. Irregular, Map like, red glazed swollen patches surr. by White border

Bg Migratory Glossitis.

Causes
- NL Regulat° (2%)
- Familial ↑
- PS.
- Atopy
- DM
- Anemia
- Reactive arthritis.

(Ambrose & Du)

(C.) Nail Psoriasis: (MSK)

mcqs:
1. occurs alone in (5-10%) of cases.
2. May associate Cut. PS. in (25-50%) of Cases.
3. ↑ be associated ⊂ PS. Arthritis in (50-75%).

. Psoriasis may affect:
- Nail bed.
- Nail Matrix

Manifestations: ± d.t ⟵ Matrix affect / Bed affect

(A) Matrix affects:
- Pitting (d.t Parakeratosis) (Most common) → most diagnostic
- Beau's lines
- Ridging
- Leukonychia (True)
- Spotted Lunula (Erythematous lunula)
- Crumbling & dystrophy.

(B) Bed affect: (1) Oil spot or drop sign:
Yellow-red Circular, Translucent areas d.t exocytosis of WBCs beneath the plate.

NB!

- Other causes of nail pitting ??
  - Traumatic
  - Alopecia areata
- How to differentiate ??
  - Ps. pitting: Large / deep / randomly arranged
  - other pitting: Small / uniform / arranged in cross hatched pattern.

(6) # of Nail Ps

- Mild affect: (ILs, Dermovate, Taz. under occlusion, Diar., ST-U)
- Severe affect: MTX, CYA, Acit, Biologics.

2. Subungual Hyperkeratosis
3. onycholysis.
4. Splinter Hge: longitudinal dark red lines due to minute foci of capillary Hge (Auspitz ✓).
5. Yellowish discoloration (d.t Sebum lipofuscin deposition)
6. Leukonychia apparent

DD: Proximal: CS(systemic)
- Endocarditis
- Vasculitis
- APS

DD: Distal
- Trauma
- Ps.
- onychom.

(D) Ps. of the Hair:
(Follicular Ps.)

- Prominent follicular involvement mainly on thighs, Elbows & Knees.

(E) Ps. of the Joints
(Psoriatic Arthritis).

- Incidence:
  - May be the only manifs in (10-15%) of cases.
  - Ass. with Cut. Ps. in (25-30%)
  - Ass. with nail Ps in (50-75%)
- Types:

Type I - Classic distal interphalangeal joint involvement (5% of patients)

Type II - Arthritis mutilans (Ass. c bone resorption & soft tissue collapse).

Type III - Symmetric polyarthritis (Rhmd like of Hands, Feet, Knee, Elbow).

Type IV - Asymmetric oligoarthritis (the most common type of psoriatic arthritis, occurring in 70% of patients) [~4 large joints affected ± c MTP, PIP & DIP affect → sausage digits]

Type V - Ankylosing spondylitis
- Arthritis of spine → lipping or Vertebral fusion (rigid or bamboo spine).

- Treatment: (1) NSAIDs ✓ (2) DMARDs: MTX, CYA, Leflunamide, Antimalarial, Sulfasalz. (3) Biologics ✓

DD: Reiter's (Reactive) arthritis.

- X-Ray
  - Most important is erosive changes of Terminal Phalanges (Acro osteolysis)
  - Tapering of Phalanges or MC.
  - Cupping of Proximal end of Phalanges (Pencil in cup deformity)

· NB: (مهم جداً)

Koebner (Isomorphic) Phenomenon: (مهم)

Def.: development ∃ the isomorphic pathologic lesions in the Traumatized uninvolved skin in patients who have a Cut. dis.

Incid: · Effect ≃ 25% ∀ psoriatic pts

onset: · occurs after aperiod ∀ 2–6 Ws following: Trauma, burn, Morbilliform Rash.

Rule: · Follows all or non Rule (if occur in one area will occur in other all areas ∉ anatomic Preferance)

Mech.: · Mech. unknown but ↓ d.t: Trauma that cause epid. & papillary dermal injury → ↑ EGF & their Receptors → Vascular & epid. changes.

Koebner:

· Reverse Koebner: Trauma → disappearance ∀ Lesions (in Ps & GA)

· it occurs in:

- Ps
- L.P.
- PRP
- Vitiligo
- EM
- Plane wart
- Mollusc um
- Pellagra
- CLS

· skin ← Darier, Kyrle's, Kaposi

· What is PseudoKoebner Phenomenon??

· Variants of Ps. Vulgaris:

1. Drug induced
2. Pustular.
3. Erythrodermic.

(1) Drug induced Ps:

- NSAIDs
- ACEI
- BB
- CCB
- INF
- ILs

(مهم)

- Antimalarial → (Erythroderma)
- Lithium
- ⊗ systemic Cs (Pustular form)

Pustular Psoriasis

- Def. psoriasis ē Macroscopic pustules. (Mac. accumulation of Neutrophils in epid.)

Types

Localized (usually Localized to hands & feet)

1. Acute → pustular bacterid
2. Chronic → Palmoplanter - Pustulosis
3. Acrodermatitis Continua of Hallopeau

Generalized

1. Acute Generalized pustular psoriasis (Von-Zumbasch)
2. Pustular psoriasis ♂ pregnancy
3. Localized pattern (not involve hands & feet)
4. Annular pattern.
5. Exanthematic type
6. Infantile & Juvenile.

- Pustular Bacterid: Bilat, Symmetrical, Acute eruption ♂ "itchy" Sterile pustules at palms & soles ē exacerbation & Remissions.

start at mid portion of hands of feet → spread to affect the whole flexor aspect ♂ palm & sole

AET + < Variant of acut exacerbation ♂ PP. Pustulosis
Reaction: (ty) Remote bacterial infection.
(So called Bacterid)

(diagnosis) → presence of Remote Bact. inf. → when Rx → Resolution ♂ the d/s. (So Rx is → Antibiotics + Anti psoriatics).

Palmoplanter pustulosis (PPP pustulosis)

- simila. to Pustular bacterid but < no inf / More chronic
- dusky Red plaques → studded ē Many yellowish pustules → dissecate → exfoliate
- pustules are seen in all stages ȳ the dis as old ones heal; New erupt. → ∴ the Condition Tend to be More chronic & persistent.
- May be ass. c̄:
  - Thyroid disorders
  - Cigarette smoking
  - Lithium
  - SAPHO syndrome.
    - Synovitis
    - acne (acneiform)
    - pustulosis
    - Hyperostosis & Osteitis:
      - Sternoclavicular hyperostosis
      - Pain & swelling of sternoclavicular or costo-chondral joint

- Tt
  1. Topical < Cs, Tacrolimus, Daivonex, Trchinoin
  2. Systemic < Acitretine, Etretinate, Cyclosporine, Colchicine, Dapsone [Antibiotics]
  3. Photo-therapy < PUVA (oral or Soak), Grenz-Zone Tt

⑥ Acrodermatitis Continua of Hallopeau: (Dermatitis Repens)

Fx < Hair / MM

- Chr., sterile, pustular Eruption affect, Initially tips of fingers or Toes
- Unilat or Bilat Asymm
- Start as: < Pustules at nail bed or Paronychia → extensio
- ē Recurrent Eruption & Crustation → : Nail dystrophy or Float away or Lakes of pus
- MM: → Geographic Tongue (لسان)
- Fate: usually Remain stable ✗ in Rare Cases → Von Zumbusch ps.

Nail bed or Fold pustules + Annulas migrans.. (Paronychia)

- DD ① Pulp inf.
② Herpetic whitlow.
③ Tinea unguium & Paronychia
④ Parakeratosis Pustulosa: Form of Eczema dermatitis ☺ usually seen in Children (Sp. Girls) (< 5 Ys) (Finger Tips)
Affect the skin around the nails & ass. ē subungual Hyperkeratosis thickened free edges & Pitting.
In this Condition: Scaling More obv than pustulosis.

سؤال

- DD of: Palmo-plantar eruptions or Pustules
① Pustular bacterid
② PP Pustulosis
③ Acrodermatitis Continua
④ Infantile Acro-pustulosis
⑤ Pompholyx (Bul. No pustules only Vesicles)

Tt < Cs Daivonex
< Sulfapyridine / PUVA
MT

Generalized Pustular Psoriasis
(Von Zumbosch)

Def: Severest form of psoriasis characterised by widespread pustules on an erythematous background due to macroscopic accomulation of neutrophils.

Genetic ↑ HLA B27

Pathophysiology (HL) ← Immunodef. ↑ Neut. Chemotaxis.

2- Enhanced polymorphonuclear leukocyte (PMNL) chemotaxis: is much more pronounced in pustular psoriasis than in psoriasis vulgaris.
*cause: either an intrinsic PMNL defect or to the presence of chemoattractants in the psoriatic epidermis. Although the principal stimulus that triggers the phenomenon of massive PMNL migration from the vasculature to the epidermis is unknown, cytokines elaborated by keratinocytes are believed to aid the process.

2- E/M: show basal keratinocyte herniations. These are cytoplasmic processes from basal keratinocytes that protrude into the dermis through gaps in the basal lamina in lesions of pustular psoriasis. These herniations mostly are clustered over collections of neutrophils in the dermis. This finding suggests an increased production of neutrophilic proteolytic enzymes in the dermis of these patients.

3- Immunohistochemical methods : have determined the involvement of some of these proteases and their inhibitors in the development of pustulation. Elastase is a proteolytic enzyme released by PMNLs during the process of extravasation and migration through the dermoepidermal junction. An epidermal elastase inhibitor, termed skin-derived antileukoproteinase, was found expressed in psoriatic skin prior to influx of PMNLs and to disappear when the composition of the infiltrate changed. This finding was not confirmed by other studies.
4- decreased natural killer cell activity in generalized pustular psoriasis.

4- ↑↑ HLA-B27 also has been found among patients with pustular psoriasis (This also is seen in psoriasis patients with peripheral arthritis, as well as in patients with ankylosing spondylitis and reactive arthritis).

**** It may start as:***

1- Pustular psoriasis from the onset (rare) (de novo)
2- As acomplication of ps. Vulgaris under certain provactive factors:

- Idiopathic.
- Infect.
- Hypocat
- Treatment:
  - Topical: → Drylands ← Zinc prith & Selsun Blue. Tar, Anthraline, Cs underocclusion.
  - Phototherapy & Photatoxicity
  - Systemic: rapid withdrawal of any systemic

- Pathology: its hallmark is presence of spongiform pustules of Kogoj ⇒ quickly become Macroscopic.

biopsy Cs

CIP:

1. General Manifs: Abrupt onset of FAHM.
2. Cut. manifs:

- Skin: preexisting skin lesions become fiery red & develop numerous pustules → then sheets of Erythema & Pustulation start to affect Non Psoriatic areas specially Flexures & Genitalia.

خطوات
lesion of skin / new lesions

- MM: Involved ē Geographic Tongue, Pustulat° & Dysphagia.

- Nails: become thickened & separated by sub-ungual lakes of pus.

طرق أو تعريف

- Fate: either
  1. Fatal: d/t exhaustion, Toxicity & Inf.

1 or 2. Remission occurs in (ds-ws) → regression to either < original Typical ps. or change to erythrodermic ps.

- Complications:
  1. death.
  2. Hypoalbummemia: d/t loss of plasma Proteins in tissues.
  3. oligemia
  4. liver → damage (d/t < digemia & general toxicity)
  5. GIT → Malabsorpt° (Dermatogenic enteropathy)
  6. Resp. → Pulm. Embolism.
  7. Skin → staphi Inf.
  8. Hair → loss (TE aft 2-3 m).
  9. Joint → Polyarthritis

INVs
- ↑ ESR
- ↑ WBCs
- ↓ Albumin
- ↓ Cat.

- Hf: 1. Hospitalizat° → Rest, Hydrat°, Bland topical Corticosteroids
  2. Acitretin → of choice. Others → Systemic Hf

(1) Generalized pustular psoriasis of pregnancy (Impetigo Herpetiformis)

dg - Special type of pustular ps. that may occur during pregnancy (d.t) high Progesterone level.

Onset - usually start at 3rd trimester (but can occur at any time) & usually persist till delivery.

Recur - Also may Recur in subsequent pregnancy or ocps.

Clp - start as: Flexural Erythema Studded pustules → Generalized pustular flare → Complications: • Toxicity • HF • RF • IUFD

Tt: (1) Termination as safe as possible.

(2) Retinoids (C.I d.t pregnancy)

(3) Cs: 1 mg/kg/day (Here is indicated while in chr. plaque ps → C.I)

(3) Annular pattern: (More chronic, less severe):

- Annular, erythematous scaly lesions & pustules at the advancing edge → Central healing & peripheral expansion.

(4) Localized pattern: (localized only to ps. lesions) (No SLM effect)

- pustules may develop at the edge or within the Existing Psoriatic lesions.
- Seen in: unstable Course of chr. plaque ps Tar use.

(5) Exanthematic type: (AGEP)

- acute Eruption of sterile pustules, abruptly appearing & disappearing
- Tt: Avoid ± d.t (Inf. / Lithium) • DD: AGEP.

(6) Infantile & Juvenile pustular ps.

- Start in 1st few wks of life.
- has benign course with No constitutional Manifs.

Erythrodermic psoriasis

(also see Erythroderma)

- def. ps. involving all or almost all of the cut. surface.
- Etiopathogenesis: may
  1. Start as 1ry manif. (rare)
  2. Complicate chr. plaque or unstable ps. Halo
     ppt by: inf., Hypocat, strong HF by Cs & tar.
  3. represent resolving pustular ps.
- PPT Factors: (as pustular)
  - inf.
  - Hypocat
  - Cs: withdrawal
  - Tar
  - Antimalarial. (Tay)
- Clue For Dx: Facial sparing & nail involvement.

Complications of Erythrodermic ps.

Treatment ↓ see Erythroderma

1. HF & myocardial dis.: d.t ↑ blood flow → ↑ CO.
2. Hypothermia: d.t Cut. VD & ↑ Heat loss
3. Hyperthermia: sweat duct occlusion.
4. Dermatogenic Enteropathy [Malabs]
5. Hypoproteinemia & Fe deficiency
6. Dehydration: d.t impaired barrier function.
7. Electrolyte Imbalance

Pathology of Psoriasis

- Parakeratosis (focal & alternating with foci of Orthokeratosis in a rhythmic fashion)
  - "Hyperkeratosis cum parakeratosis"
- Hypogranulosis
- Acanthosis.
- Rete Ridges → لمبة نازلة
  (Psoriasiform Hyperplasia)
  - Regular Elongation: Test-Tube like
  - Clubbed (Thickened lower ends)
- Dermal papillae: (earliest feature)
  - Elongated, oedematous & dilated Tortous capillaries. (= Auspitz Sign)
  - Thinned Epid. above them (Thinned st. Malpighii)

: 2 Neutrophilic accumulations: "لمبة نازلة"

↓ d.t migrat of Neutrophils from the dilated capillaries in Dermal papillae.

① In st. Corneum: occurs in all cases of Ps. & called "Munro Microabscesses"

② In st. Malpighii (Prickle Layer): occurs only in pustular ps. & called "Spongiform pustules of Kogoj"

↓

"multilocular pustules surr. by Sponge-like network made of Flattened KCs."

D.D of Microabscesses

① Munro: Ps, SD, Acrodermatitis continua & Reiter's

② Pautrier: Mononuclear cells + MF cells in St. Malpighii (in MF)

③ Papillary → Neutrophils: In DH
→ Eosinophils: in B.P

④ Subcorneal: Candida, Impetigo,

⑤ Kogoj: CPS & [illegible]

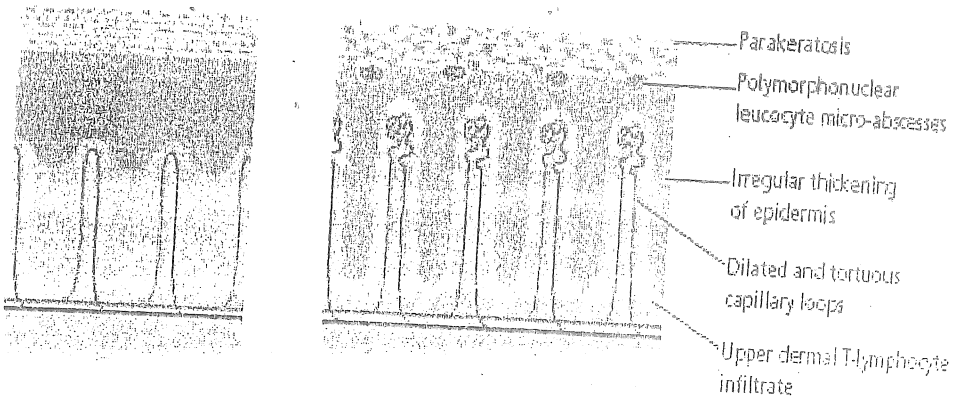


Fig. 5.1 Histology of psoriasis (right) compared with normal skin (left).

Investigations Recently recommended.

- BP Assessment.
- W.t "
- Lipid Profile
- Insulin Resistance (IR) | Metabolic Syndrome.
- ECG.

Ocular Psoriasis

- Ectropion & Trichiasis
- Conjunctivitis & Keratitis
- Corneal dryness / Melt.

Co morbidities.

- Ps Arthritis
- HTN
- obesity
- CV dis
- DM
- Crohn
- Liver dis.
- Psychological

Treatment of PS.

(1) General Measures: → to comorbidities ↓ Po- وتقليل العوامل

- ↓ weight
- stop smoking "سم" & Drugs as -- ??
- Avoid < stress / Trauma
- Fish oil Dietary supplementation (Max-EPA 3 cm/d

(2) Medical therapies:

1. Topical:
   - Cs. < Topical ILs.
   - Opt.
     - Calcipotriol
     - Tazarotene
   - Opt.
     - Tar
     - Anthralin
     - Salicylic acid 3%

2. Phototherapy:
   - PUVA
   - UVB — NBUVB, Excimer light, Balneotherapy, Climatotherapy.
   - PDT ← "photodynamic"

3. Systemic therapy:
   - Methotrexate
   - Acitretin
   - Cyclosporine A.
   - Biological Therapy.

4. Other therapies — Combination: Rotational, Sequential

- Severity تحديد

(i). BSA
(ii). Local
(iii). Symptoms
(iv). ?? Psychosocial
(v). Physical, Financial & Emotional Impact

Choice of Tt

↓

Psoriasis

- **Mild** (≤ 2% of BSA) → **Topical**
- **Moderate** (3–10% of BSA) → . Topical ± . Systemic . Photo
- **Severe** (>10% of BSA) → . Topical ± . Systemic . Photo

Topical Tt

- **Indications** (1.) as a monotherapy in mild PS
  (2.) as a combination in Mod–Severe PS

- **Mechanism:** (طرق - آليات - تأثيرات)

"عادة" any Topical Acts on one of the Following mechanism:

1. ↓ KC prolif. (Anti prolif.)
2. ↑ KC maturation (Differentiation)
3. Immunomodulation. (Anti inflammatory)

Mild–Mod

- Cs, Tar & Anthraline < 1/3
- Calcipotriol : 3 mechanism
- Tazarotene : 1 & 2

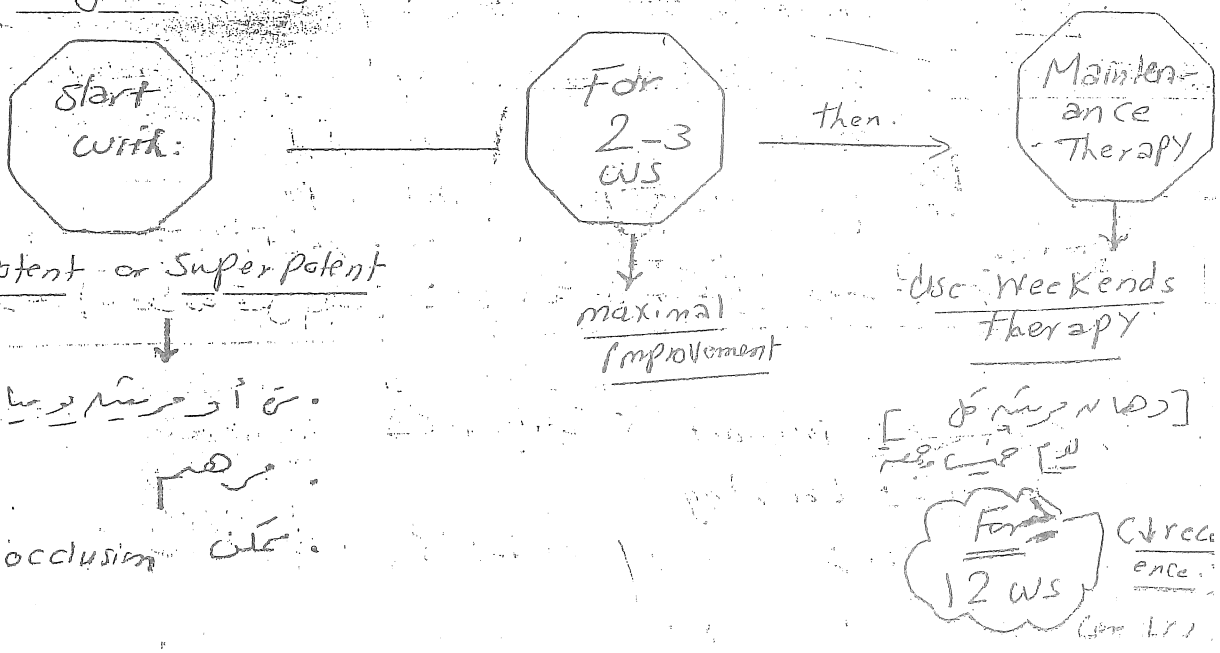
- Monoth.
- 1st line < Ct calcip.
- 2nd : other

Severe Ps :

- Topical عيّنات : (5)
  - Indicat
  - Mech.
  - SE
  - CI
  - How to Use
  - Preg.

Topical Cs < Topical / Intra lesional for < Nail dis.

- Indications: ① mild psoriasis: as 1st line monotherapy
  - ② Moderate-severe Ps: in combination ē other ↑ systemic therapies
  - ③ Face & Flexural Ps (other Topicals are Irritants) ← Monoff
  - ④ Recalcitrant plaque lesions (used under occlusion ⓐ ±L.)
- Mechanism ① ↓ Kc prolif. ② Immunomodulation (↓ inflamm) ← by binding To GRE (gluco. Corticoid Response Element).
- Regimen (نظام العلاج)



- NB: ① once 1day is as effective as twice/day
  - ② Face & Flexures → Hydrocortisone 1 (↓ inflamm ē out Effect on prolif.).

- S.E: ... ↑ Tachyphylaxis → Lack ē effect after repeated use
  - To avoid: weekend Ht ē change Type
- C.I: ① infection ← Bact. / Viral / fungal
  - ② Atrophy
  - ③ CD.

Vit. D3 analogues

- Calcipotriol (calcipotriene) = (50 µg/gm)
- Maxacalcitol
- Cacitriol (Sirkis) → active form of vit D3.
- Tacalcitol (Curaloderm)

- **Indications:** See 1 & 2 in Cs.

- **Mechanism:** (3)
  1. ↓ KC prolif.
  2. ↑ KC differentiation
  3. Immunomodulatory → (++ cornified envelop formation & ++ Transglutaminase)

Hyperprolif. keratins.

- ↓ K6, 16 & 7 (1-2 ws)
- ↑ K1, 2, 10 (2-3 ws)
- ↑ IL10 & ↓ IL8
  - IL10: immune suppression, antiinflam.
  - IL8: inflam. Cy to KCs → ↑ KC prolif

- **S.E:**
  1. irritation (in face & Flexures)
  2. with S.A → inactivation of Calcipotriol.
  3. with N.B-UVB or PUVA → degraded brit & at same time act as photoprotective so preventing its effect.

(i) Irritant (ii) Drying (iii) Combined

- **R:** لذا: لازم إستخدامه قبل الجلسة بفترة أكثر من ساعتين أو بعد الجلسة

- **C.I**
  1. Pregnant (Category C)
  2. Lactating
  3. > 100 gm/w (أكزيما، أنثونة، دانيونكس/إكزيم) (Hypercalcemia may occur) ē dose < 100 gm/w
  4. Renal dysf. (عشان ما ↑↑ Ca+)
  5. Hypercalcemia (عشان Ca++ or bone metabolism) (Sarcoidosis)
  6. Allergy

How to use (Regimen)

1. as Monotherapy
2. with Cs → ... طبعاً
3. ē photo therapy
4. ē systemic Therapy.

How to use it in psoriasis ??

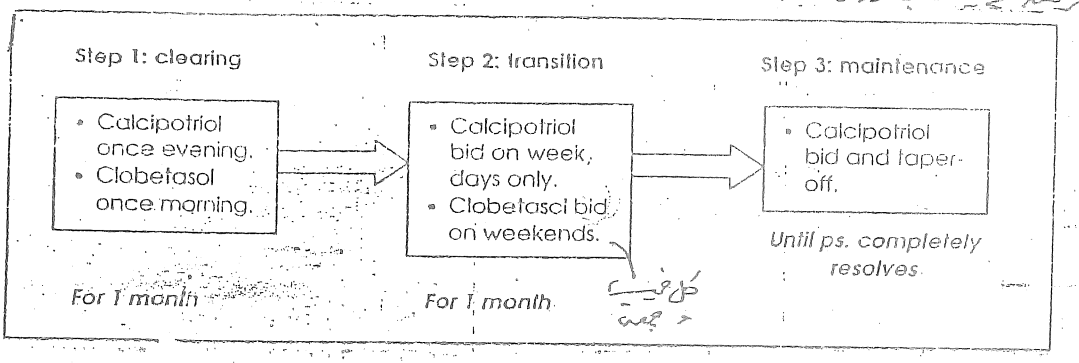
① as a monotherapy : وحده مع أدوية بديلة

Good in Face & Flexures (to avoid Cs S.E but ± irritant).

② With Cs: "طبة" الأصل (a) (d)

(a) Daivonex لوحده + Dermovate مساء

(b) Sequential therapy : يوم الصبح Diav. + Cs مساء
Diav. مساء بدون Cs



(c) Pulse therapy : على الـ Daivonex طول الأسبوع. (Weekends) في آخر الأسبوع Dermovate

(d) Combination therapy : (Daivobet) oint.

: Diav. 50 µg/gm + Betamethasone dipropionate 0.5 mg/gm.

→ rapid onset of action superior to either calcipotriol or betamethasone diproprionate alone. The challenge was to combine a Vit. D3 analogue (works optimally at alkaline pHs) & a corticosteroid (works optimally at acidic pHs) while maintaining stability & achieving optimal bio-availability

+ (e) Maintenance therapy : (To Perform long Term Remission) وحده مع أدوية بديلة (بعد فترة من العلاج بالكورتيزون) لفترة عكس تصل لسنة

NB = may be used under occlusion.

③ with Phototherapy (Cas in vitiligo)

بعد الجلسة.
قبل الجلسة بفترة قصيرة عشان ؟!

(why)

Calcipatriol ⟶ (photoprotective) ⟵ phototherapy

Photodegradation.

④ With MTX, Acitretine or CyA: Combined will then to ↓ dose of these drugs & ↓ S.E.

جديد من Tazarotene (Zarotex gel) ®

- The only Topical Retinoid used in ## & PS. (all others are not effective).
- Mechanism: binds to Retinoic acid Receptors: RAR-(β & γ)
  → (1.) ↓ KC prolif. (-- glutaminase & K16)
  (2.) ↑ KC differentiate
  (3.) Immunomodulation (±)
- Indications: mild PS. as 2nd line ## as monotherapy or in combination in phototherapy
- C.I: 1. Erythrodermic ps.
  2. Progressive unstable ps.
  3. pregnancy & lactation
- SE → ACD (contact dermatitis) & Teratogenicity

Retinoics ← تحت (C).
Category X)

- How to use (Regimen): ??
  (1.) alone; but ! irritant
  (2.) with Cs: mometasone furoate (< ↑ efficacy ↓ irritation)
  (3.) with UVB (↓ UVB dose by ≃ 1/3 to avoid burning)
  (4.) with 5-FU: for warty ps. (التركيبة)

Allow Topical phototh
Cs & FU

- Efficacy: moderate (50% improvement in 50% of cases after 6 wks & ##).

Limitation
- BSA: maximum use & it for (10-20%) BSA
- duration: for upto 1 year.

nail psoriasis

mild → few new

severe → acitretin

→ methotrexate

no effect of photo therapy.

Tar & Anthraline

Tar (Crude Coal Tar)

- Mech. (1) Antiproliferative
  (2) Anti inflammatory
  (3) Antipsoriatic
  (4) Antimicrobial (Bacterial)

- Use either:
  - Alone ± Cs or Goeckerman Technique
    - Tar + UVB (Suberythem)
    - يدهن الـ Tar بتركيز معين بكمية كبيرة ثم يعرض للأشعة بجرعات زيادة تدريجية
  - Then → Anthralin (Twice daily in Lassars paste, S.A, Zinc oxide, + Paraffin).
    - Tar (bath) + UVB
    - light for 5-30 mins then washed

- Indications: as Anthralin

- C.I: as Anthraline + pregnancy (C)

- S.E
  - irritation, staining of clothes
  - bad odour
  - folliculitis
  - Acneiform Eruption

- Polytar shampoo
- once hair plus

- لتين ٢ حالات أساسية:
  - scalp ps.
  - الي معاها حرشة

Anthraline (Dithranol) (Micranol 1% C)

Mechanism (1) ↓ KC prolif.
(2) Immunomodulation:
- -- Neutrophil Chemotaxis
- ↓ IL1 & 6.

use: either:
- Ingram Technique (odious) : Tar (bath) + UVB
- or Short contact therapy (0.5-2') (to ↓ S.
  - light for 5-30 mins then washed

Indications: mild to moderate or severe psoriasis:
2nd line ## as mono. therapy or in combinat

C.I
1. Pustular ps
2. Erythrodermic ps.
3. Progressive unstable ps.
4. Hypersensitivity / Excoriated skin.

S.E: irritant & staining → clothes / skin (Purple/brown)

Efficacy: Very effective.

Pregnancy: Category C

Collomac → SA 16.7%

Other Topicals

- Salicylic acid
- 5. FU
- Calcineurin inhibitors (for Face & Flexural ps)
- Moisturizers

* Salicylic acid *

- Mech. ① Keratolytic
  - ↓ cholesterol sulfotransferase
  - ↓ cholesterol sulfate formation
  - ↓ Solubilization of intracellular cement substance
  - ↓ Loss of cellular Adhesion
  - ↓ Keratolysis.
- ② Mild Anti-inflammatory
- ③ bacteriostatic & Fungistatic
  - by -- of panthoenic acid.
- Concentration: 0.5% – 40%.
  - <5% → keratolytic
  - scaling dis. → 1-5%
  - Wart: 10-40%
- S.E (depend on Conc. & Surface area & application)
  - ① irritation, Erosion, Ulcerate
  - ② Systemic absorption (salicylism)
    - specially infants & newborn
    - → Neurological & GIT Toxicity.
  - ③ Pregnancy (Category C): may
    - Cause Premature closure of ductus arteriosus → pulm HTN
    - (when used in late pregnancy)

- 5 FU (0.5-5%): -- enz. thymidylate synthetase → -- DNA synth.
  - Treatment of wart ps.
  - 1% 5 FU + Tazarotene 0.1% (Co-Gel) ← كريم بالله

ecrine = eccrine

Phototherapy

- Indications: → Mod. - Severe Ps.
  1. Ps. vulgaris affecting ≥ 3-10% of BSA as 1st line Month ± in Combinat. ē Topicals.
  2. When systemic therapy is C.I ✓

A. PUVA [unknown Mech.] ← Antiprolif. Anti inflamm.
   1. Antiprolif. (by -- DNA replicat.)
   2. affect cytokines release.

B. NBUVB [unknown ?]: ← anti inflamm ←
   → 1. Antiprolif. (-- DNA replicat. by formats of Pyrimidine dimers] → -- Cellular prolif.
   2. ↑ PGs
   3. ↓ ILs: 12, 18, 23 & ↓ Th17.
   4. ↓ NK cells
   5. -- APCs.

C- BALNEOPHOTOTHERAPY (Dead Sea therapy): Empirically, it has been known that the combination of salt-water bathing and sunlight exposure is an effective treatment for psoriasis. From studies at the Dead Sea, it became clear that highly concentrated salt water (>20%) together with UVB light is most effective.65 This therapeutic strategy also was termed balneophototherapy; it has become increasingly popular in Europe, where concentrated salt-water baths together with artificial UVB sources are used in psoriasis treatment centers. A possible mechanism of concentrated salt-water bathing is the elution of biologically active peptide mediators and enzymes such as human leukocyte elastase from the inflamed skin.

D- Heliotherapy (also called climatotherapy): makes simple use of intentional direct exposure to natural sunlight to get the therapeutic benefits of the included ultraviolet radiation. The use of heliotherapy began a long time ago when it was used in India, China and Egypt to treat diseases, including psoriasis. Ancient Greeks also used natural sunlight as therapy. As far back as 3,000 years, medical practitioners were advanced enough to use sunlight-sensitizing chemicals before sun exposure - a primitive version of today's photochemotherapy or PUVA. Heliotherapy has been studied, and it works. Benefits lasting beyond a year have even been documented.

Systemic Therapy

- Indications:

IF

- Ps. is moderate-severe: defined as:
  - Psoriasis Vulgaris ≥ 3-10% BSA or
  - Pustular psoriasis (Generalized or Localized)
  - Erythrodermic Ps.
  - Psoriatic arthritis (mod-severe)
  - Severe Nail ps.
- Phototherapy is:
  - C.I
  - Failed (Resistant)
  - Inappriak (Ps. Arthritis & Nail) also - pustular / Eryth

- So if Ps. is: Moderate-severe → Phototherapy

If: C.I / Failed / Inappriate (nail ps. / Ps. Arthropath)

→ Systemic therapy (MTX, Acit. & Ciclosp)

Systemic therapy: if Failed / C.I → Biological Therapy

The treatment must not be Worse than the disease.
"Side effects are often the limiting factor in psoriasis treatment"

Systemic steroids are condemned in psoriasis.

Methotrexate (Amethopterine)

- Introduction, Basic & Mechanism:

• Folic acid (vit M) & Folate (anionic form) are Forms of vit. Bc.

- Metabolism: (① Folate → ② DiH. folate → ③ Tetra H. F. → Purine)

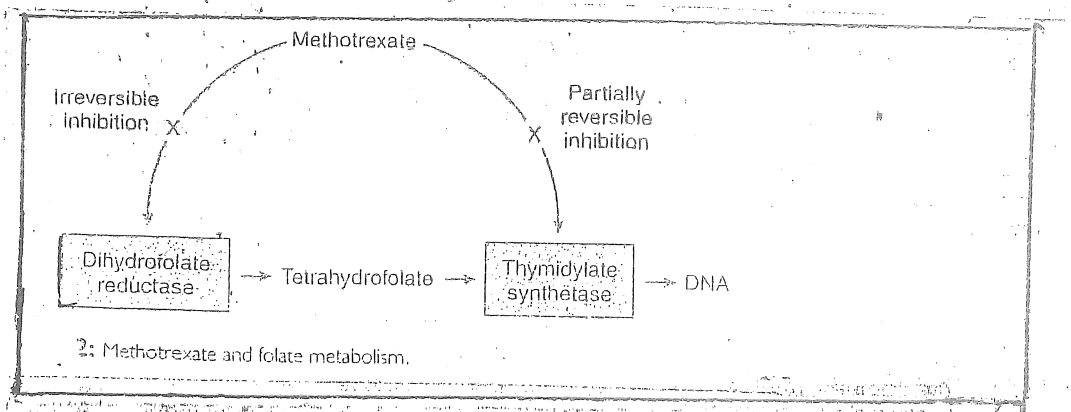
Folic acid (Folate) —Reduced To→ Dihydro folate (DHF)

—Reduced by enz. DHFR (dihydrofolate reductase)→ Tetrahydro folate (THF)

THF —Thymidylate Synthetase enz.→ Purines, Thymidylate

Purines → • DNA & RNA Synth (Cs → cell division during S phase)

Thymidylate → -- 2 enz. 2 times
① DHFR → Complete irreversible
② Thymidylate Synthetase → Partial irreversible
→ -- DNA & RNA Synth.



2: Methotrexate and folate metabolism.

• This Inhibition is Competitive because Structure of MTX similar to DHF but & vary higher affinity to the DHFR enz.

• This inhibitory effect is very Marked on highly dividing Cells (BC, Lymphoid Cells, BM cell & Mg Cells).

• Mechanism of Action: (Psoriasis) ← Antiprolif by -- KC prolif.
Immunos. by -- Lymph. ↓
Anti-Inflamm. by -- SAM.

① Anti proliferative (in large doses for Cancer Rx):

. -- of Cellular Prolif. (KCs, Lymphocytes, BM Cells & Mgs Cells).

Through: inhibition of 2 enzymes ← DHFR & Thymidylate synthetase

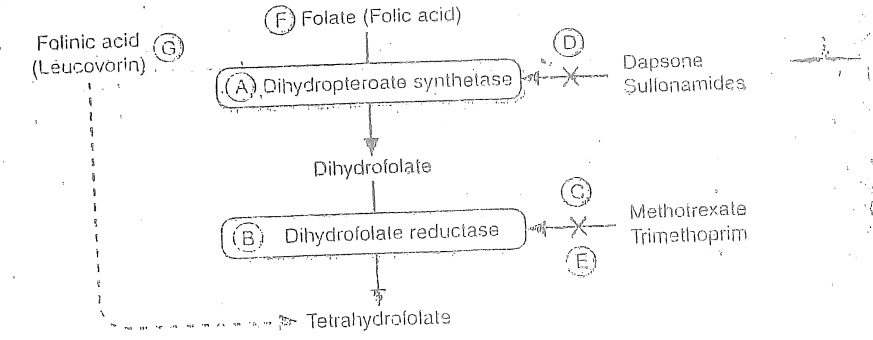
کارڈیکٹر نہ دہ سیکلیزمنے ہے۔ Ps
وہ ہے --KC prolif
وکن تاثیر ہے
KCs سے زیادہ T Cells

② Immunosuppressive: (In Psoriasis)

. -- Lymphocyte prolif. (Long Time Point > Eff. on Lymph. on K
. -- " Trafficking..
. ↓ Neut. Chemotaxis.
. ↓ Histamine release.

③ Anti-inflammatory:

. ↓ SAM (S adenosyl methionine) → ↑ add
→ ↓ inflamm.
. through its Immunosuppressing effect.



* In general, this metabolic pathway is more important to the adverse effects of methotrexate (including drug interactions) than it is for drug efficacy. The fully reduced tetrahydrofolate is important for subsequent pyrimidine nucleotide synthesis.

A Folate (folic acid) is initially reduced to dihydrofolate by dihydropteroate synthetase.
B Dihydrofolate is further reduced to tetrahydrofolate by dihydrofolate reductase.
C Methotrexate inhibits this pathway through competitive inhibition of dihydrofolate reductase (DHFR).
D Dapsone and various sulfonamides inhibit dihydropteroate synthetase, and thus, can amplify the inhibition of DHFR by methotrexate.
E Trimethoprim (including fixed combinations with sulfamethoxazole) also inhibits DHFR, and thus can amplify the inhibition of this pathway by methotrexate.
F Folic acid given in therapeutic doses essentially competes with methotrexate for DHFR, ↓ the adverse effects of methotrexate by ↑ tetrahydrofolate production.
G Folinic acid, in a sense does an "end run" around the methotrexate inhibition of folate, serving as a fully reduced substrate for pyrimidine synthesis.

Figure 8-3: Methotrexate and folate metabolism, drug interactions of importance.

Dosage & Administration:

- **Preparations:**
  - MTX tab. 2.5 mg.
  - MTX injection: (50 mg/1 ampul)
- **Routes:** oral, IM, IV & (Topical)
- **Doses:**
  - 5 - 30 mg/W
  - Psoriasis usually improve @ 15-25 mg/W
  - usually don't exceed 30 mg/W.
  - in children: 0.2 - 0.4 mg/kg/W.

MTX: لا يعطى يوميا

- **Method:**

[Doses < 20] → **Oral** (Triple Week Schedule)

given as:

3 divided doses (5 mg)

at 12 hrs apart / Week.

(8 am → 8 PM → 8 am)

Parenteral

IM or IV

- **Indications:** ← GIT ↓ Abs.
  - ① If the oral dose needed to be > 20 mg/W (at this dose → absorption is poor)
  - ② Erythroderma: d.t malabsorption.
  - ③ Severe GIT symptoms

- **NB.** Mid week schedule is Toxic (Not used) [تعطى بجرعة كبيرة]

(I. Regimen) (تابع الفصل)

PreTH invs are NL → Start with Test dose 5 mg (لازم يبدأ بجرعة صغيرة)

(To avoid Idiosyncatic Pancytopenia)

→ Repeat
- CBC (يومي)
- Liver
- Kidney

(BM is highly active and abnormals as pancytopenia may appear in 7 ds)

if No detected Abnormalities

Give 7.5 mg / w → gradually ↑↑ the dose by 2.5 mg / w (depending upon efficacy & (S.E)) (usually at 10–25 mg/w)

Note: Efficacy
- onset 2–6 w.
- Maximum 12 w.

Results:

Good Response that maintained for 1–2 ms → gradual tapering by 2.5 mg / w (وقد ما توصل لأقل جرعة متحافظ إياها)

Bad Response → ↑ the dose gradually by 2.5 mg / w (Not > 30 mg/w)

NB: (if you on oral & dose Needed is > 20 mg/w → (Shift from oral to IM or IV)

لازم تعطى:
Folic acid 1–5 mg / day (ليس حاجة لو بيعطى ميثوتريكسات MTX)

or

give folic acid 5–7 mg / w (AAFP 2000)

Why؟
1. ↓ GIT upset
2. ↓ Blood Complicat (Pancytopenia)

Indications, C.I, S.E, Monitoring Guidelines

Box 8-1: Methotrexate Indications and Contraindications

FDA-approved dermatologic indications
Psoriasis[18]
Sezary syndrome[17,66]

Off-label dermatologic uses

Proliferative dermatoses
Pityriasis rubra pilaris[25–27]
Pityriasis lichenoides et varioliformis acuta[28,62]
Reiter's disease[29]

Immunobullous dermatoses
Pemphigus vulgaris[30–33]
Bullous pemphigoid[31–34]
Cicatricial pemphigoid[35]
Epidermolysis bullosa acquisita[36]

Autoimmune connective tissue diseases
Dermatomyositis[37–41]
Subacute cutaneous lupus erythematosus[42]
Systemic lupus erythematosus[43]
Systemic scleroderma[44]
Morphea/localized scleroderma[45–47]

Vasculitis and neutrophilic dermatoses
Leukocytoclastic vasculitis[48]
Cutaneous polyarteritis nodosa[19,30]
Behçet's disease[50]
Kawasaki disease[51]
Pyoderma gangrenosum[52,53]

Dermatitis
Atopic dermatitis[54,55]

Other dermatoses
Sarcoidosis[56–60]
Keloids[61]
Lymphomatoid papulosis[62]
Keratoacanthomas (intralesional)[63]
Mycosis fungoides[65,66]
Cutaneous Crohn's disease[67,68]
Chronic idiopathic urticaria[69]

Contraindications[19]
Absolute
Pregnancy (X) → بالحمل
Lactation
Relative

♀ → ذكرها أنثاري ← ٦-٣ شهور بعد وقف
♂ → يستعمل لعازل لـ ٣ شهور (Teratogenic)

- CBC: Severe Impairment.
- Liver: disturbed enzs, Active hepatitis, Cirrhosis, Hx of liver dis.
- Renal: Impairment (Cc. clearance < 60 ml/min) (↓ dose)

- Others:
  - Alcoholics
  - D.M
  - obesity
  → High risk For Complicat.
- Immunodeficiency (HIV)
- Inf. < Active inf. or Hx. of serious
- Active PSU.

(مع TB)

Pregnancy Category "X"

- S.E of Methotrexate:-

Most frequent[14]	
Nausea	
Vomiting	
Abdominal pain	
Fatigue	
Headache	
Occasional	
Dizziness	
Loss of libido	
Impaired memory	

1. Subjective.
2. CBC: Pancytopenia.
3. Liver: Hepatitis & Cirrhosis.
4. Lung: pneumonitis (Acute onset Cough & dyspnea).
5. Mucocut (Skin):
   - Alopecia
   - Photosensitivity
   - oral ulcers
   - Tenderness / Necrosis of plaque.
   - Others (rare): Urticaria & Angioed, Vasculitis.

⑥. Preg. & Lactat:

- Abort
- Teratogenicity
- G.R.
- Cancer.
- Immunosupp.

⑦. Idiosyncrasy [Early in the course with Full dose — Test dose]

- Pancytopenia
- pneumonia
- GIT Hge.

- Risk of Pancytopenia:
  - Early Full dose.
  - No folate.
  - Elderly
  - Renal
  - Interact: (NSAIDs, Sulfa, Dapsone)
  - Dose
  - Low albumin
  - 1st 4 wks.

⑧. Carcinogenesis:

- SCC in PUVA
- Lymphoma (in RA pt)

⑨. opportunistic Inf:

- Pneumocystis Jirovecia
- Cryptococcosis.

• Monitoring Guidelines:

• Baseline = pre-Rx

CBC, Liver, Renal: (before Rx)

- SGOT
- SGPT
- 3 viruses
- Albumin. (if ↓ → ↑ risk of Lung Complications & Toxicity.)
- BUN
- S. Creatinine
- Cl Clearance.

CXR → if previous Hx of chest dis.

Preg. Test → if in child bearing period

HIV test: → in risky pt. (Homosex.)

Follow-up (during Rx)

- CBC: every 2 weeks for 2 months, then every 3 months
- Liver: every 2 weeks for 2 months, then every 3 months
- Renal: every 3 months

Liver Biopsy

- After every 1.5–2.0 g total dose for low-risk patients
- After every 1.0 g total dose for higher-risk patients
- Every 5 months for patients with grade 3A liver biopsy changes

- Alcoholics
- Diabetics
- obese
- Hepatitis (HCV, HBV) non active
- Hx of Liver dis.
- Hepatotoxic Drug
- Hx of familial liver dis.

(FITZPATRICK) Classification of Histologic findings of liver Biopsy (of MTX ##)

Grade	Histologic findings:
. I	[. NL liver
. II	[. any of the following / fatty liver. / nuclear variability / Portal tract. Expansion / inflamm. & Necrosis.
. IIIA	[. Mild fibrosis. (Fibrotic septae extend to lobule
. IIIB	[. Mod. – Severe fibrosis
. IV	. . Cirrhosis

What's your decision ??

. . Grade: I, II → Continue ##.

IIIA → Repeat Biopsy ein 6 m.

IIIB & IV → Stop ##.

هل ممكن نستغني عن الـ Biopsy
بتحليل آخر؟؟

Yes by Repeated assessment of
Amino terminal Pro Collagen III

* Drug interactions with MTx: →

هون في عوامل ممكن تأثر على
الأدوية بشكل عام - أدوية الكلية

. الأدوية
. Dapsone
. Sulfonamides
. Trimethoprim
. NSAIDs

Also TMP+SMx → -- DHFR
→ Additive toxicity

Table 8–1: Drug Interactions—Methotrexate

Interacting drug group	Examples and comments
These drugs may ↑ methotrexate serum levels (and potential toxicity)—displacement from plasma protein	
Antibacterial—other	Chloramphenicol
Antibacterial—tetracyclines	Doxycycline, minocycline, tetracycline
Anticonvulsants	Phen, Val
Antipsychotic agents	Phenothiazines (various)
These drugs may ↑ methotrexate serum levels—↓ renal excretion and displacement from plasma proteins	
Antibacterial—sulfonamides	Sulfamethoxazole, others (including TMP/SMX combination)
Anti-inflammatory drugs—other	Salicylates
NSAID (including COX-2)	Various; different NSAID with varying ↓ methotrexate renal excretion
These drugs may ↓ methotrexate serum (or intracellular) levels—other mechanisms	
Antibacterial	Ciprofloxacin, penicillins
Antiplatelet drugs	Dipyridamole; ↑ intracellular accumulation of MTX
Miscellaneous drugs	Amiodarone (mechanism unknown), probenecid; ↑ intracellular accumulation of MTX, also competes with methotrexate for renal tubular secretion
Methotrexate may ↑ serum levels (and potential toxicity) of these drugs	
Bronchodilators—xanthines	Theophylline
Methotrexate may ↓ serum levels of these drugs (loss of efficacy)	
Cardiac drugs—inotropic	Digoxin
Pharmacodynamic interactions—drugs that inhibit these enzymes markedly ↑ risk of hematologic toxicity	
Dihydropteroate synthetase Dihydrofolate reductase	Dapsone, sulfonamides (notably sulfamethoxazole in TMP/SMX combination) Trimethoprim, trimetrexate; inhibit same enzyme as methotrexate
Pharmacodynamic interactions, additive effects—drugs with inherent risk for hematologic toxicity	
Antiviral agents	Cidofovir, interferons, zidovudine
Immunosuppressive agents	Azathioprine (see below)
Other drugs with similar effect	Chemotherapeutic agents, clozapine, lamotrigine, etc.
Pharmacodynamic interactions, additive effect—↑ risk of hepatotoxicity	
"Alternative" medical therapies	Black cohosh, kava
Habits	Alcohol (excessive)
Retinoids—systemic	Acitretin, bexarotene
Other interactions of potential importance involving methotrexate	
Antibacterial—other	Aminoglycosides; may ↑ anti-tumor effects of methotrexate
Immunosuppressive agents	Mefacept, azathioprine, corticosteroids, cyclosporine, efalizumab, leflunomide, mycophenolate mofetil, sirolimus, tacrolimus; may ↑ opportunistic infection
Nutritional supplements	Folinic acid (Leucovorin); combined use may ↓ methotrexate efficacy (generally considered that folic acid does not have this same inhibitory effect)

MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drugs; TMP/SMX, trimethoprim/sulfamethoxazole.

Adapted from Facts & Comparisons, The Medical Letter Drug Interactions Program, E-pocrates, and other references on pg. xvii in the Preface.

Over dosage

(Methotrexate Toxicity)

- MTx Toxicity may occurs in the following conditions:

1. ↓ renal Function.
2. daily Ingestion.
3. Concomitant use of Folate antagonist as TMP+SMX ✓

- Treatment → (1) folinic acid supplementation (Leucovorin) (Fully reduced, Functional Folate Coenzyme)

Conversion To THR directly without need for DHFR Enzyme.

→ (2) Thymidine: if given it will Converted to thymidylate under effect of Thymidine Kinase enz. without need for Thymidylate Synthetase enz.

HL

Dose: Start Immediately with 20mg (10mg/m²) either oral or IV & assay MTx level / 18-24hrs.

MTx level	Leucovorin
0.5×10^{-6} M	20 mg / 6 hr
1×10^{-5} M	100 mg / 6 hr
0.2×10^{-5}	200 mg / 6 hr

Acitretin in PS

- 2nd generation Retinoids (Monoaromatic) → Etretinate ✓ / Acitretin
- Mechanism
  1. ↓ KC prolif.
  2. ↑ KC differentiation (Maturation)
  3. Immunological & Anti-inflammatory
- Dose & Administration:
  - dose: 0.5 – 1 mg/kg/d.
  - In PS: usually start ē 10 – 25 mg/day & ↑ gradually to avoid Flare of Ps. at start ← Hi
- Indications: as MTX (but Acitretin is the ## ∂ choice ∂or Pustular Ps)
- Pre ## Screening: (5) (pds)
  - Liver functions
  - Kidney "
  - Lipid profile
  - Glucose (..ow)
  - pregnancy test "أهم واحد"
  - Spinal XRay (CDISH) (لما توقعت انه الحالة ما عندها لفترة طويلة / تشخيص أو ل ٢ سنين)
- During ## Monitoring:
  - Liver & Lipid profile → كل ما بدأنا له شهر وبعدين كل ٣ شهور بعدين
  - Kidney: (For Elderly & those ē mild to med. dysf.)
  - Hyperostosis: → Hx → XRay: مرة كل سنة
  - Pregnancy test "لازم كل شهر"

. S.E & C.I → See Therapy

Administration: as
- Mono-therapy
- + PUVA [RePUVA]

. Re-PUVA = Retinoid PUVA

PUVA ← استيرتين

- ✓ Effective > PUVA alone or ACIT.
- ✓ ↓ PUVA dose.
- ∴ ↓ Aging & Cancer caused by PUVA

.NB: ص. حبة نظف ..

Isotretinoin (Neotex)

Is Acitretin وإلى نتائج نفطة بدل سم.

. DISH : Diffuse Idiopathic Skeletal Hyperostosis

. Def Type of degenerative arthritis

. Ch By : Bony, Tendons & ligaments Calcification

. CIP : Pain & Stiffness of Neck & Back.

. X-ray: Calcification & (±) Bony Spurs

CYCLOSPORINE

Introduction: Cyclosporine, a cyclic peptide of 11 amino acids, was isolated from the soil fungus *Tolypocladium inflatum Gams* in 1970 and was found to have clinical immunosuppressive effects in 1976. In 1979, during a rheumatoid arthritis trial, it was discovered that cyclosporine improved cutaneous psoriasis in patients with psoriatic arthritis.

Two forms are available:

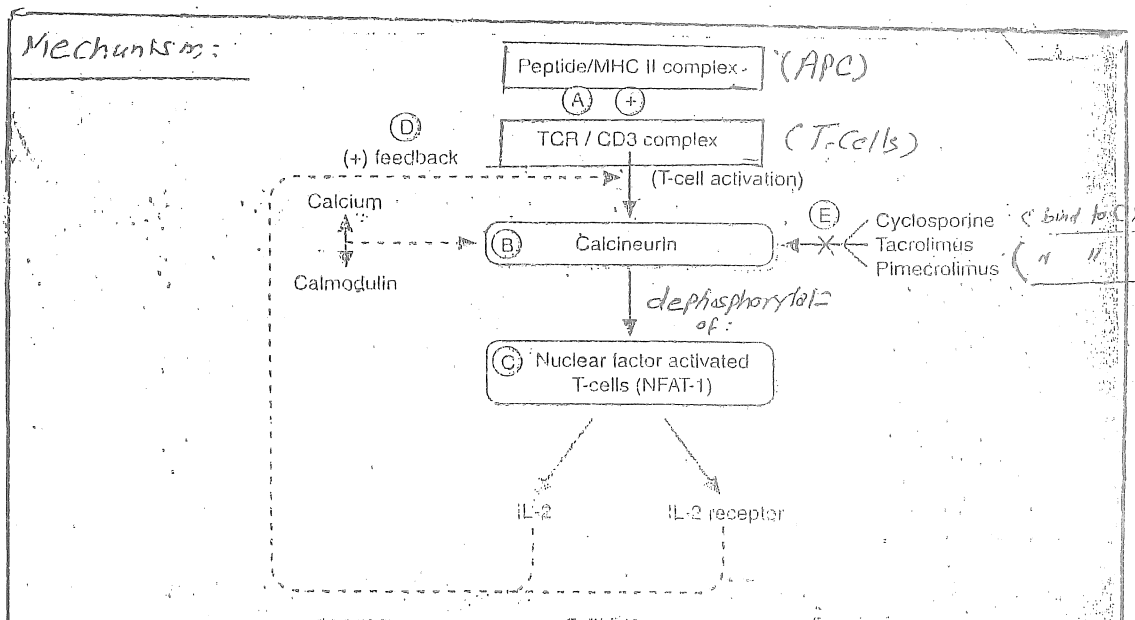
1- (Sandimmune®): 20 and 100 mg Caps.

2- (Neoral®): Predigested microemulsion that is more completely and consistently absorbed: (25 mg, 100 mg) or as an oral solution (100 mg/ml)[12]. The solution can be mixed in orange juice or apple juice, but grapefruit juice should be avoided because it alters cyclosporine's metabolism (see Ch. 131).

Pharmacokinetics:

* Metabolism: by the CYP 3A4 pathway,

* Excretion: is via bile and feces (Only 6% of cyclosporine is excreted unchanged in the urine)



* This calcineurin/"signal 1" system creates a highly efficient immunologic response to various antigenic (or superantigen) stimuli.
A The peptide/MHC II complex on the antigen presenting cell interacts with the T-cell receptor (TCR)/CD3 complex and results in T-cell activation; ↑ calcineurin activity is one result of this T-cell activation.
B With calcium as a cofactor, and through interaction with the calcium binding protein calmodulin, calcineurin ↑ activity of the transcription factor NFAT-1.
C NFAT-1 ↑ formation of both the cytokine IL-2 and the IL-2 receptor.
D Through subsequent binding of IL-2 to IL-2 receptor, the T-cell activation is further amplified.
E Cyclosporine (as well as tacrolimus and pimecrolimus) inhibits the key enzyme, calcineurin, in this system with ↓ IL-2 and ↓ IL-2 receptor production, with the [illegible] "signal 1".

• Mechanism: (on T-Cells)

1. Binds to cyclophillin Rs → ↓ Calcineurin protein → ↓ IL2 product & ↓ IL2 Rs Expression → ↓ T cell prolif.
2. ↓ IFN-γ product → ↓ ICA-M 1 Expression → "↓ T-Cell Trafficking."
3. Binds to steriod Rs ass. heat shock protein 56 → ↓ IL 1, 4, 5, 6, 10, TNF α.

• Indications: (CCE) دواء

Box 11-1: Cyclosporine Indications and Contraindications

US FDA-approved indications : - Psoriasis if:

1. Severe psoriasis
2. Recalcitrant, treatment-resistant psoriasis
3. Disabling psoriasis (including localized versions such as hand-and-foot psoriasis)
4. Major life events

Approved indications in other countries* (Australia and European Union)

Psoriasis
Atopic dermatitis[5–8]

Off-label dermatologic uses

Papulosquamous dermatoses
Lichen planus[9–13]

Bullous dermatoses
Pemphigus[14–18]
Pemphigoid[19–22]
Epidermolysis bullosa acquisita[23]
Linear IgA bullous dermatosis[24]

Autoimmune connective tissue diseases
Dermatomyositis[25–27]
Lupus erythematosus[28]
Scleroderma[29–32]

Neutrophilic dermatoses
Behçet's disease[33]
Pyoderma gangrenosum[13–16]

Neoplastic
Sézary's syndrome
Mycosis fungoides

Dermatitis
Atopic dermatitis[5–8]

Alopecia
Alopecia areata[37]
Lichen planopilaris[38]

Granulomatous dermatoses
Granuloma annulare[39–41]
Sarcoidosis[42]

Disorders of keratinization
Pityriasis rubra pilaris[43,44]

Photosensitivity dermatoses
Chronic actinic dermatitis[45]

Other dermatoses
Eosinophilic cellulitis[46]
Kimura's disease[47]
Morphea[48]
Prurigo nodularis[49]
Papular erythroderma of Ofuji[50]
Persistent papular acantholytic dermatosis[51]
Purpura pigmentosa chronica[52]
Reiter's syndrome[53]
Scleromyxedema[54]

Urticaria
Chronic urticaria[55–57]
Cold urticaria[58]
Solar urticaria[59]

Contraindications

- uncontrolled HTN
- Renal impairment
- liver ↓
- phototherapy (Mech. of Contra)
- Mg (Past or present Hx)
- pregnancy
- Lactat
- Marabs.
  - Active Inf.
  - Drug interact

Pregnancy prescribing status—category C

- FS ← Severe Recalcit Disabling Major life.
- AD

Dosage & Administration:

Administration: Cs A may be used as:

1. Monotherapy.
2. Sequential therapy
3. Rotational therapy →

1) As a Monotherapy: (2.5-5 mg/kg/d) ref

Dosage: (Systemic) (2.5-5 mg/kg/d)

- Moderate PS: 2.5 mg/kg/d → ↑ gradually (by) (0.5 mg/kg/d) Every other week till either:
  - → Satisfactory Response
  - → Maximum dose Reached 5 mg/kg/d.
- Severe PS: start ē maximum dose: 5mg/kg/d.
  - if → improvement → Taper by 0.5 mg/kg/d every 2ws (EOW) till minimum effective maintenance dose is Reached.

2) Sequential therapy: CyA → improvement → Add Acit. or MTX & tapper CyA by ≃ 1 mg/kg/d → Maintain Acit. or Re-PUVA.

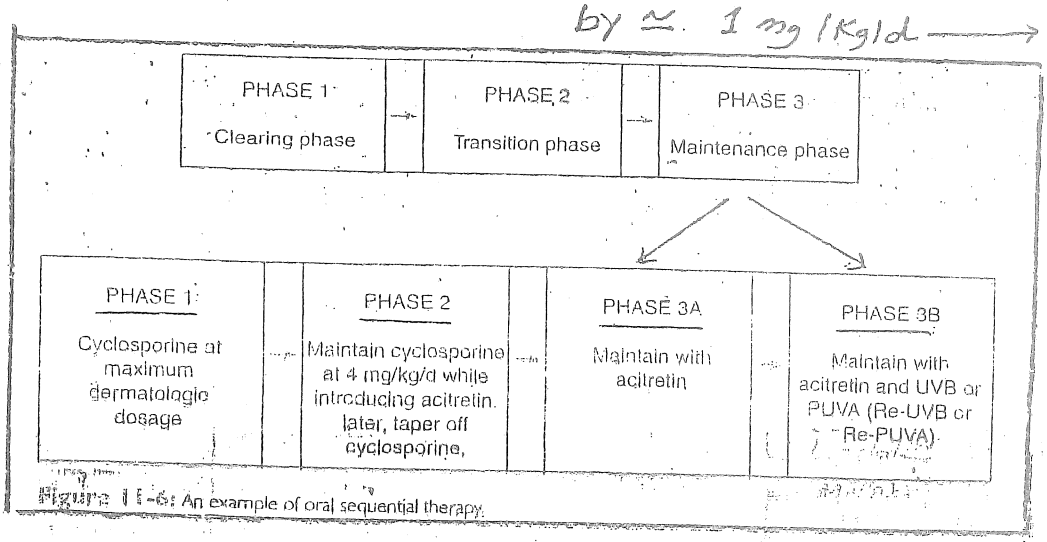


Figure 11-6: An example of oral sequential therapy.

3) Rotational therapy → see below. (عند)

S.E:

① The Most important:

(c) [HTN (25%, mild, reversible)
- Nephrotoxicity (sp. > 2 yrs)

2 Hyper - Hypertrichosis & Hyperplasia of Gums.
- Mg (scc, lymphoma) → (Sa) not used c phototherapy
- Electrolytes. (3 Hyper + 1 Hypo).
  3 Hyper: •K •Uric a. •lipids
  1 Hypo: Mg

② Other S.E:

- GIT: NVD.
- Neuro: Headache & Tremors.
- Musculoskeletal, Arthritis & Myalgia.

---

3 • Contraindications: (Old)

(py) [
- uncontrolled HTN.
- Renal impairment.
- Hepatic "
- Current or PH. of Excessive phototherapy ?? (↑ Mg risk)
- Mg
- pregnancy & lactation (C)

• Drug interactions: (CsA Metabolised by hepatic CYP3A4)

(A) inhibitors of CYP3A4 → ↑ CsA level:

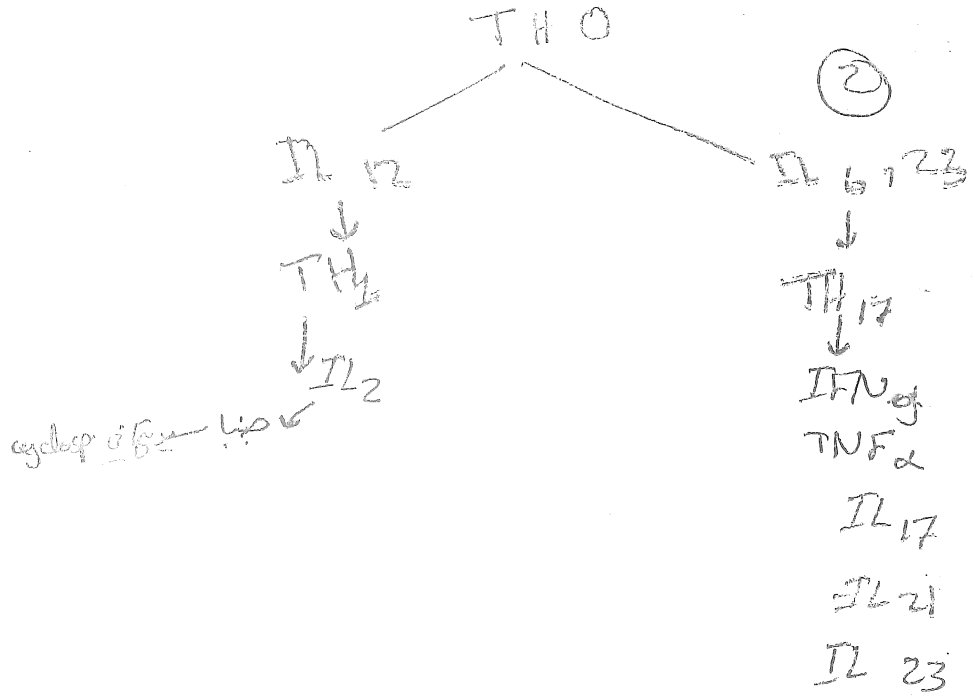
CsA is Metabolized by Cyp 3A4 & also inhibit it

Antib:
- Erythromycin
- Cipro.
- Cephalosporins
- Doxy.

- Protease inhibitors
- CCB
- Cimetidine

Grapefruit.

Antif:
- Ketoconazole, Itra/Fluc.
- SSRIs


TH0
IL 12
TH1
IL2
IL 6, 23
TH17
IFNg
TNFα
IL17
IL21
IL 23

(B) CYP3A4 Induces ⟶ ↓ CsA level:

- Rifampicin
- Gr. seofulvin
- Bexarotene
- Carbamazepine
- Nafcillin
- Tetracycline

(C) Drugs that may ↑ risk of Nephrotoxicity.

- Aminoglycosides
- TMP/Smx
- NSAIDs
- Immunosuppressives

• Monitoring Guidelines: (see S.E)

(InVs)

Pre ## Screening

- HX & exam: To exclude < HF / Tms
- B.P قياس
- Kidny function T. (BUN & Mc. urine exam.)
- Liver.
- CBC.
- uric acid, Magnesium & Electrolytes & lipids.
- pregnancy test.

during ## Monitering

(as in pre ## screening).

"ينشرف المريض كل أسبوعين أول شهرين ثم كل شهر مع متابعة الضغط والتحاليل"

if ## for > 6ms:
1. Creatinin clearance
2. CsA level
- Renal Biopsy (rare). Needed

NB: 1. if HTN occured: → (give CCB):

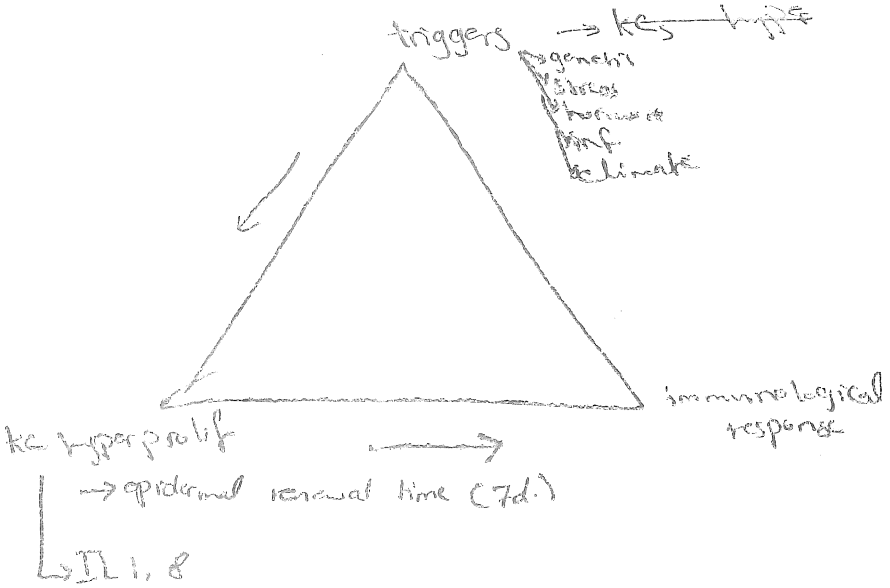
لو اضطر
لو ريتش

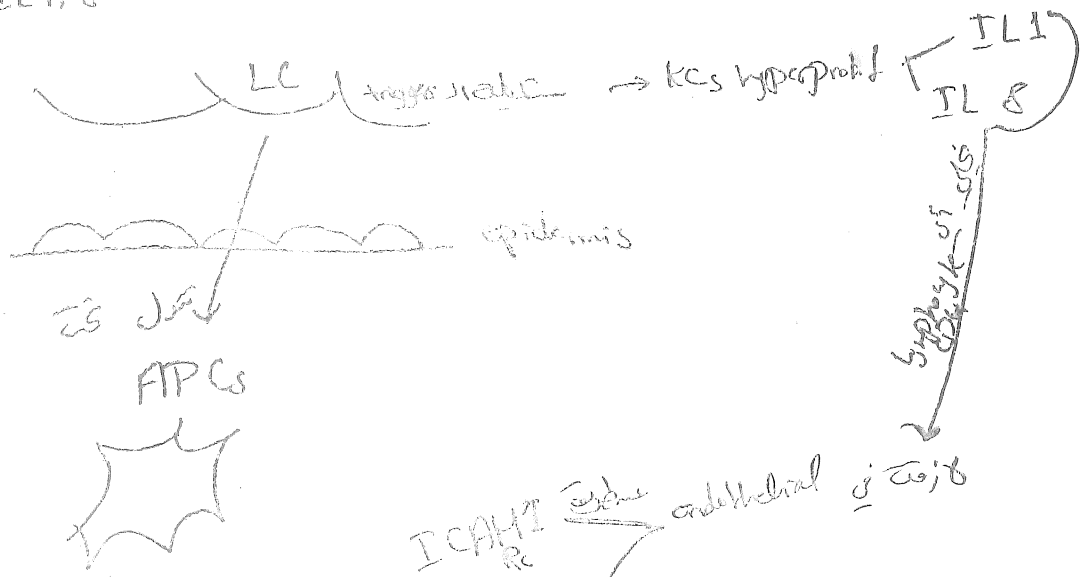
(DHPCC's) → . Nifedipine
. ISradipine (better > Nifd. because dont cause gingival Hyperplasia).

Avoid: . diltiazem & Verapamil (Not recommended d.t alteration of CsA level).

* avoid (K+) sparing diuretics Why ??

Pathogenesis





ICAM1 kc → adhesion

T-cell → Trapping of CD4

IL8 ↳ neutrophil chemotaxis

(CD4

LFA1 ↔ ICAM1

LFA3 ↔ CD2

(CD8)

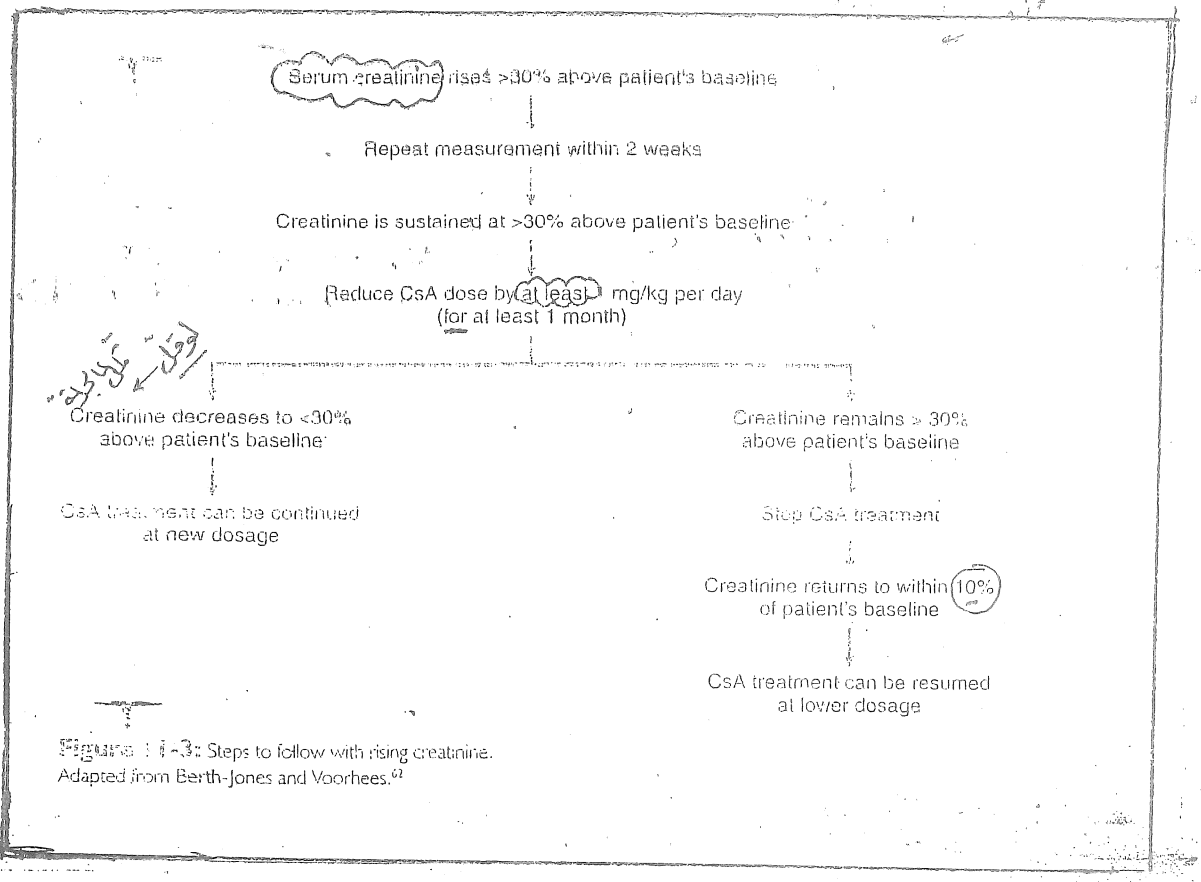


Figure 11-3: Steps to follow with rising creatinine. Adapted from Berth-Jones and Voorhees.[61]

NB

CsA

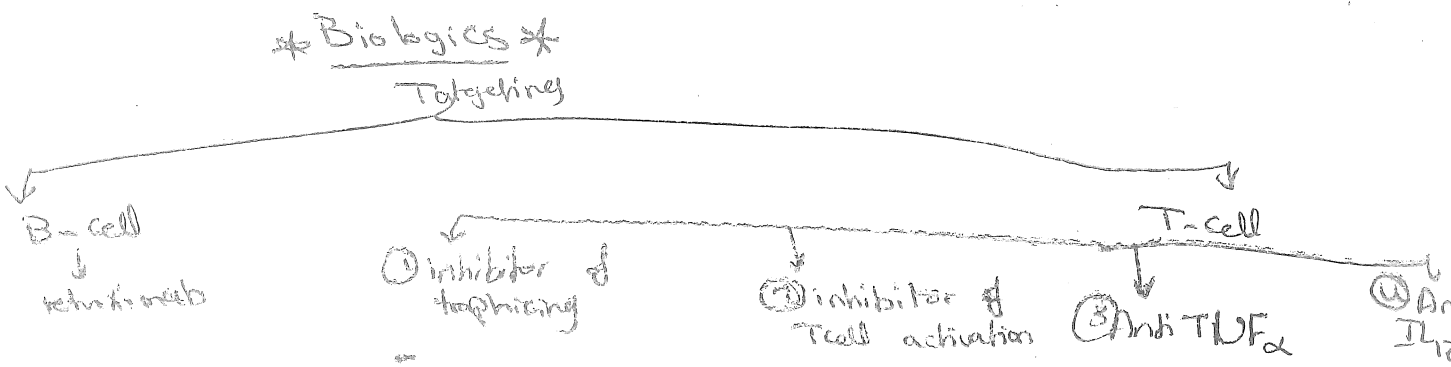
- Rapid Clearing
- ↑ Hair growth
- effect Kidney
- ↑ K+ & ↓ Mg+
- Preg.(C)

Acitretin

So:

- Slow Clearing (used to maintain Clearance induced By CsA)
- ↑ Hair loss.
- No effect on Kidney.
- -Ve.
- Preg. (X)

But Both ↑↑ lipids.


* Biologics *
Targeting
B-cell
① inhibitor of trafficking
② inhibitor of T cell activation
③ Anti TNFα
T-cell
④ Anti IL17

Biological Immunotherapy (Targeted Immuno modulators)

(Bioengineered Immunomodulators)

Def. ⇒ Bioengineered Molecules that Target Specific steps in Pathogenesis of several immune mediated disorders

as:
- Psoriasis
- Ps. arthritis
- Rhoid arthritis
- pemphigus
- Crohn's
- B cell Lymphoma.

They work by one or more Mechanisms:

1. Elimination of pathogenic T. cells
2. -- T cell activation
3. -- T cell Trafficking
4. -- Cytokines (TNF-α)
5. changing the immune profile from (Th1) → Th2
6. Eleminating Pathogenic B cells.

Biological Immunotherapy may be directed against

- Pathogenic TS cells.
  - Inhibitors of T. cell Trafficking
    - Efalizumab
  - Inhibitors of T-cell Activation
    - Efalizumab
    - Alefacept
    - Ustekinumab
  - ③ Anti-TNFα
    - Etanercept
    - Infliximab
    - Adalimumab (humera) 2500 L.E
  - ④ Anti-IL 17 → Secukinumab 9000 L.E
- Pathogenic B cells
  - Rituximab
    - used in: B cell Lymphoma, Rhoid arthritis

• Inhibitors of T-Cell Trafficking

• Efalizumab

↓

Anti CD 11a

(CD11a is a component of LFA-1 on T cells & Endothelium).

↓

Blocks interaction bet LFA-1 (on T cells) & ICAM-1 (on Endothelium)

T cells → -- activation

Endothelium → -- Trafficking

∴ So, Efalizumab has double Mechanism of Action

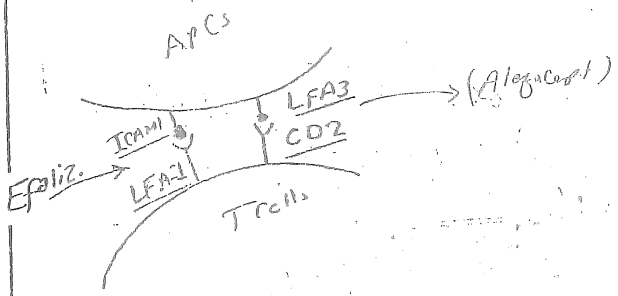
• Alefacept

↓

Anti CD_2

↓

So Blocks Interaction bet CD_2 (on T cells) & LFA3 (on APCs)



• What is the composition of these Molecules??

① Alefacept → Human fusion protein = LFA-3 + IgG-Fc

يتكون من جزء من CD_2 فيمنع ارتباط CD_2 بـ LFA_3 (الذي في APC)

② Efalizumab → Humanized (mouse + Human) monoclonal Antibody that block CD11a → -- LFA-1 & ICAM-1 interaction.

• Efalizumab : Severe Neurological complication (PML) تم سحبه من السوق سنة 2009

• Alefacept : Risk of Mg تم سحبه من السوق سنة 2011

Biologics : أدوية

CEPT

Fusion protein

IgG1

Alefacept

as in ~~etanercept~~

IgG1

LFA3

bind to CD4

Etanercept

IgG1

TNF α Re

TNFα يمتص

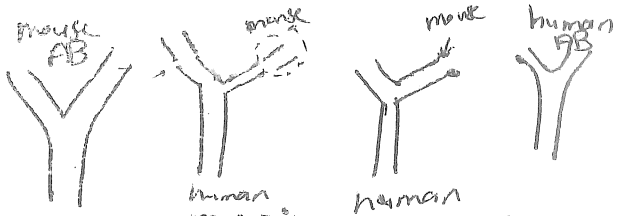
in circulation

MAB

* monoclonal AB

Ab نقية واحدة

→ Blocking AB



① ~~Ximab~~ → monoclonal AB from mouse

② ~~Umab~~ → from human

③ ~~Xizumab~~ → kimeric

④ ~~Zumab~~ → humanized

mouse → allergy

kimeric

Xolair → omalizumab →

allergy تحسس ضد IgE بيعمل

Anti TNF-α

Etanercept
- Fusion protein Composed of: (TNF-α Receptors) + IgG1-Fc
- TNFα ← يمسك ب
- اللي في الدم وبالتالي يمنع ارتباطها مع مستقبلاتها الموجودة على سطح T cell.

Infliximab
- Chimeric Monoclonal Antibody That binds to TNFα → prevent interaction of TNFα with their Receptors.
- يشتغل بنفس الميكانيزم لكن تختلف في التركيب.

Adalimumab
- Human Monoclonal Antibody To TNFα, Thus preventing their interaction & surface Receptors.

Block diff of TH1

- Ustekinumab: Anti IL12 & 23 → TH17 diff ↓ IL17

NB
- Alefacept & Etanercept → Fusion protein
- -mab → Monoclonal Antibo.

الفرق

كده اتكلمنا عن الميكانيزم والتركيبة

(-cept = fusion protein)
(-mab = Monoclonal Ab Block)

Agent	Target (Anti:)	Structure
Alefacept	CD2	• Fusion protein
Efalizumab	CD11a (Part from LFA-1)	• Humaized (zumab) Clonal Ab.
Etanercept	TNFα (soluble form)	• Fusion protein.
Infliximab	TNFα (soluble & memb. bound)	• Chimeric Antibody (ximab)
Adalimumab	TNFα (sol. & bound)	• Human Antibody (umab)
Ustekinumab	Anti P40 Subunit of IL12/IL23	• Human Antibody. (umab)

Discussion of

- Indications.
- Contraindications (C.I)
- S.E
- pre-tt invs (Baseline)
- during tt Monitoring (Follow up)
- Doses
- ورا الاسلاد

Indications in Ps:

1. Mod_severe Ps. Eligible for Systemic therapy
2. When Systemic tt ← Failed or Contraindicated (Pregnancy, Liver)
3. Psoriatic arthritis: after failure of DMARDs (Disease modifying anti Rheum Drugs)

Contraindications

General

- **Absolute**
  1. Inf (Viral, Bact (TB), Fungal)
  2. ↑ Risk of Sepsis
  3. Immunosuppression
  4. Hypersensitivity
- **Relative**
  - Pregnancy ← Anti TNF & Alefacept (B), Efalizumab (C)
  - Malignancy (PH ⑧ Last 5yrs)
  - Excessive use of Photo-Chemotherapy (BCC or SCC زيادة)
  - Hepatitis B ⇐ Give tt or Prophylaxis to prevent Reactivation

Selective

- **Efalizumab:** leukocytosis, lymphocytosis or Thrombocytopenia
- **Alefacept:**
  - CD4 < NL
  - HIV → CD4 ↓
- **Anti TNFα:** Autoimmune
  - ANA +ve CTDs
  - AICTD
  - CHF
  - MS (also use in MS)
- Blood dyscrasia
- Ustekinumab
  - BCG in the past 12 ms.
  - live attenuated vaccine

• Side effects.

- **Alefacept** →
  - Local Reactions at Site of inject. (Commonest)
  - ↑ Mg. Risk.
  - ⇐ CBC ⇐ ↓ Plt
- **Efalizumab** →
  - Flu like Symptoms (Fever, Headache, Pain, Chills, GIT dist.) → Common in the 1st few wks.
  - Blood Toxicity (Hemolytic anemia & thrombocytopenia).
- **Etanercept** →
  - Local Reactions at Site of Injection (Commonest) (Erythema, pruritus, pain & swelling)
  - Reaction
  - infection
  - Lymphoma
  - L.E. (Anti-TNFα induced SLE)
  - opportunistic Inf. (±)
  - Lymphoma (±) & other Mgs.
  - L.E
- **Infliximab** (Enhances)
  - Infusion-Related Reactions (Commonest): (itching, urticaria, pain, Hypo TN & HTN)
  - infection: pneumonia, cellulitis & sepsis.
  - Lymphoma & Mg (±)
  - L.E. (±)
- **Adalimumab**
  - inf.
  - Lymph.
  - LE
  - ↑ incid. of Mycobact. Inf. & opportunistic Inf.
  - Lymphoma & Mg (±)
  - LE (±)

Reaction
- Local
- Systemic

Inf. opp. (Mycobact.)
Mg & Lymphoma
LE. drug induced Lupus

Efalizum → Sepsis, Viral Meningitis, Hemolytic an... Leukoencephalopathy (Cerebral meningitis)

Pre-Tt Assessment (Base line Inv.)

- Efalizumab & Alefacept → CBC & differential T cells (CD4)
- Anti TNF-α → Tuberculin Test (Mantoux) or Quantiferon-TB Gold
  - chest X-Ray (optional)

During Tt Monitoring (Follow up Inv.)

- Alefacept: CD4+ assessment — (كل ٣ شهور)
- Efalizumab: CBC (كل شهر)
- Anti TNF-α: Tuberculin test & CXR (كل سنة)

Doses (لكل: Etanercept, Ustekinumab, Adalimumab) (SC)

- Alefacept < IM (15 mg) or IV (7.5 mg) — كل أسبوع لمدة ١٢ أسبوع، تابع كل ٤ أسابيع بعد كده
- Efalizumab: SC. 1 mg/kg/w. (for 12 wks)
- Etanercept (Enbrel): SC. 25 mg Twice/w for 12 wks, then 50 mg/w. (for 12 mths)
- Infliximab: slow IV infusion: 5-10 mg/kg at 0, 2, 6 wks then /8 wks
- ✓ Adalimumab: 40 mg SC/2w
- Ustekinumab < ≤100 Kg: 45 mg SC 4w dose then /12w; >100 Kg: 90 mg (Cosentyx)
- ✓ Secukinumab: 300 mg SC at 0, 1, 2, 3, 4 wks then 300 mg/4 wks

- 2 EV → SC
- Alefacept → IM or IV
- Infliximab → IV

- Alefacept: Amevive®
- Efalizumab: Raptiva
- Ustekinumab: Stelara
- Etanercept: Enbrel
- Infliximab: Remicade
- Adalimumab: Humira
- Secukinumab: Cosentyx

Rituximab

- **Def** → Chimeric Monoclonal Antibody, against CD20 (IgG1) on the surface of B cells.
- **Mechanism:** Binds to CD20 → B cell apoptosis & depletion (NL & diseased) (Not plasma cells)
  - ↓ Complement mediated Antibody ↓
- **Indications:**
  - B Cell Lymphoma.
  - Rhoid arthritis.
  - FDA: Wegner's granulomatosis, Microscopic PA (Poly angiitis) → (Cs)
  - Pemphigus (vulgaris & Paraneoplastic)
  - Bullous pemphigoid (BP)
  - SLE.
  - DM.
  - Vasculitis.
- **Dosage:**
  - Lymphoma: ~~375~~ mg/m² for (IV) for 1–2 ms
  - Rh. Arthritis: 1000 mg IV for 2 wks
- **S.E:**
  - Anaphylaxis & death: in 24 hrs.
  - ARF
  - SJS
  - TEN: Toxic epidermal necrolysis
  - Mg
  - 0 thes
  - FAHM, Chills
  - Itching
  - Rash
  - Urticaria & Alopecia.
- **CI** →
  - Allergy
  - HBV.
  - Cardiac pt.
  - Inf.

CI ē Active Inf.

Leflunomide

ex: Arava (R) (Arava Avar)

- one of DMARDs: "Disease Modifying Anti Rheumatic Drugs"

- Indications: (1) Rheid Arthritis.
  (2) Psoriatic "
  (3) Psoriasis.

- Mechanism: -- dihydroorotate dehydrogenase → -- pyrimidine synth → Antiproliferative.

- dose: 100 mg Id for 3 days, then 10-20 mg Id
  - Response: ē in 4 wks
  - Maxim. " : 4-6 wks.

- S.E: GIT
  - Pruritus, Rash, HTN.
  - Hepatotoxic.
  - Alopecia.
  - Pancytopenia.

- Liver
- CBC

البتريط ٣ شهور ← 100 mg تعطى ثم بعدين 10 mg كل يوم

Indications of Systemic Cs in Ps

(1) Persistent uncontrolable Erythrodermic Ps. causing Metabolic problems
(2) GPP: if other lines failed or C.I
(3) Pustular Ps. & pregnancy
(4) Hyperacute Poly arthritis.

Other therapies

1. Combination
2. Rotational
3. Sequential

1- Combination

Contraindicated combinations

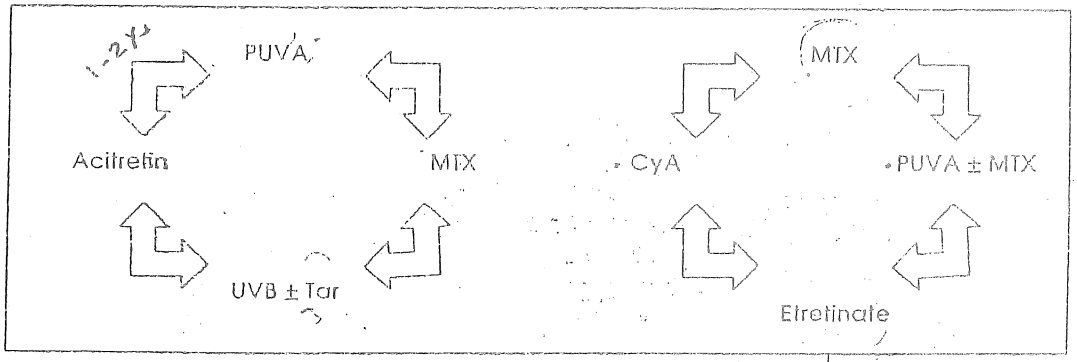
- Acitretin and CyA? Accumulation of CyA (cis) CyA inactivation by cytochrome P-450 system can be inhibited by acitretin.
- Hydroxyurea & MTX or azathioprine.
- CyA + PUVA ? ↑ occurrence of SCC. ← MTX & PUVA → SCC
- Cola tar + PUVA? Significant phototoxic responses.

Combination with the biologics

- Etanercept + MTX, CyA, Acitretin.

2- Rotational therapy in psoriasis

- This facilitates long-term treatment & minimizes chronic toxicity by rotating to different treatment regimens before significant "individual drug" toxicities occur.



Selection of rotational therapy

- Each of the 1st agent therapies (PUVA, methotrexate, etretinate, UVB & cyclosporine), should be used in rotation for only 1-2 yrs to avoid the risk of appearance of side effects, e.g. skin cancer with PUVA.
- If a pt was able to tolerate 2 or 3 of the therapies, it might take 4-6 yrs before returning to the initial treatment, thus reducing the cumulative toxicity from each individual therapy.
- If the 1st agents are no longer effective, then 2nd agents should be considered.

3. Sequential therapy

Calcipotriol

cyc + Acitretin

Example of PASI score

	Head & Neck	Upper ext.	Trunk	Lower ext.
Erythema (0-4)	4	4	4	4
Scale (0-4)	4	4	4	4
Induration (0-4)	4	4	4	4
Sum (E+I+S)	12	12	12	12
Body surface area (1-6)	6	6	6	6
Sum x Area	72	72	72	72
Area multiplier	0.1	0.2	0.3	0.4
Sum x Area	7.2	14.4	21.6	28.8
PASI total	72			

BSA: (0)=None, (1)=<10%, (2)=10-30%,(3)=30-50%, (4)=50-70%, (5)=70-90%, 6=90-100%

PASI

- 1–10 Mild
- 10–20 Moderate
- >20 Severe
- PASI 75 75% improvement in baseline PASI
- PASI 50 50% improvement in baseline PASI
- Static indicator: Only indicates disease severity at time of scoring
- Internal consistency is essential

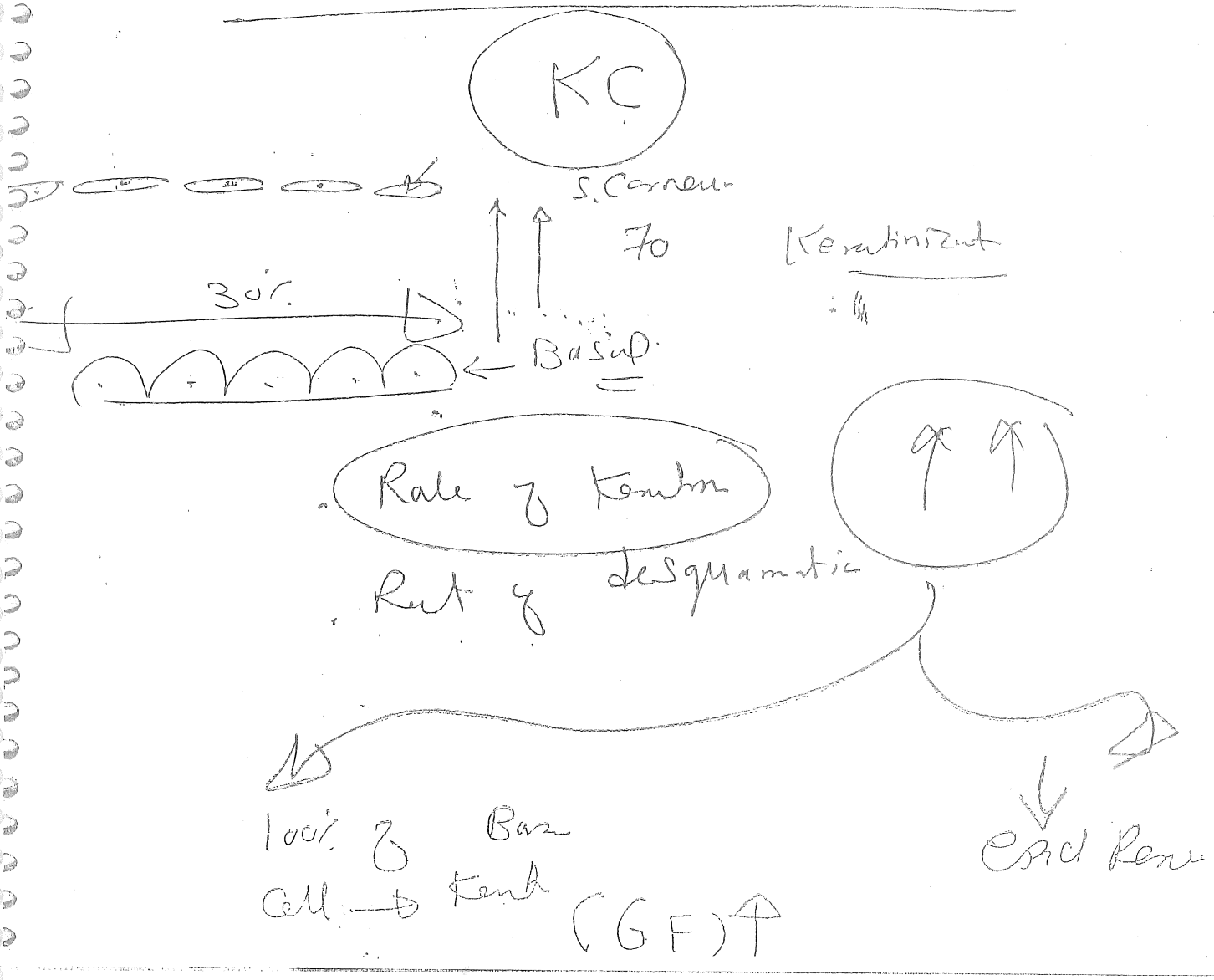
2. Stress : Substance P (Capsin)

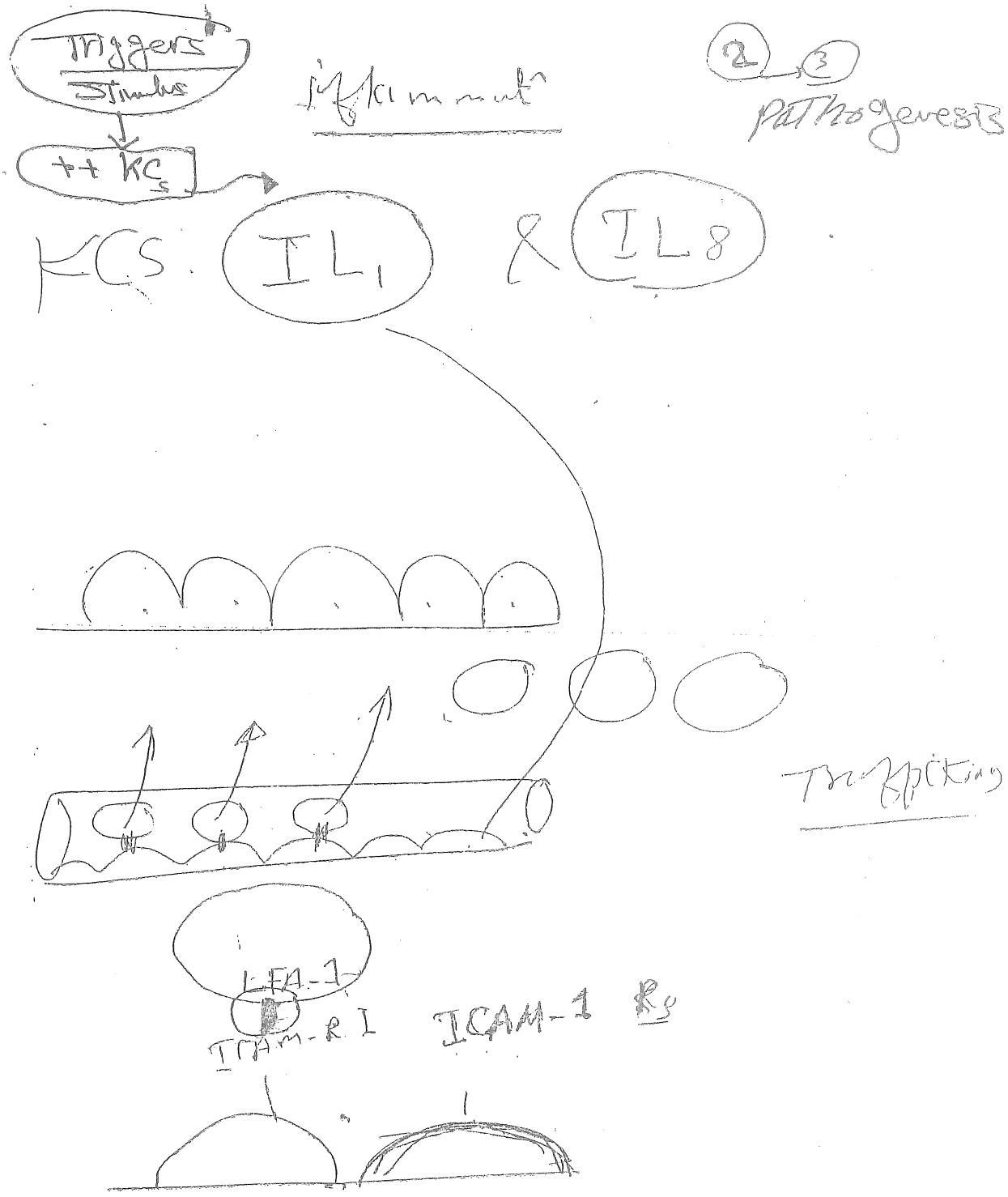
3. Inf

4. Trauma

5. Climat :

6. Hormones

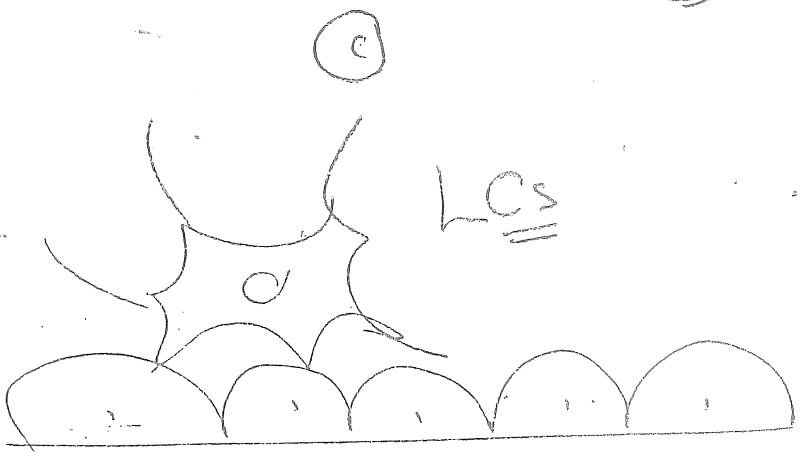


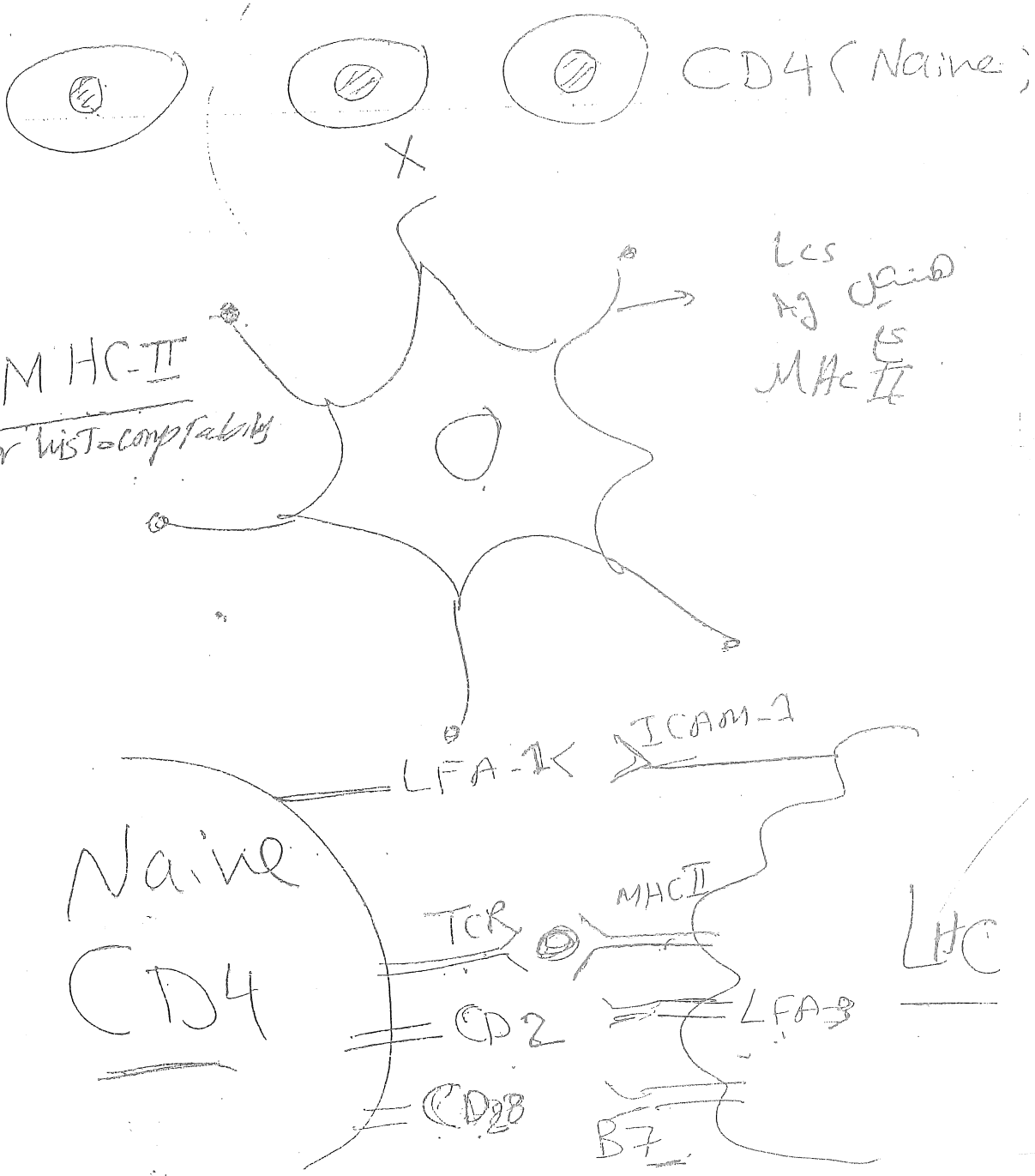


. 5-10%

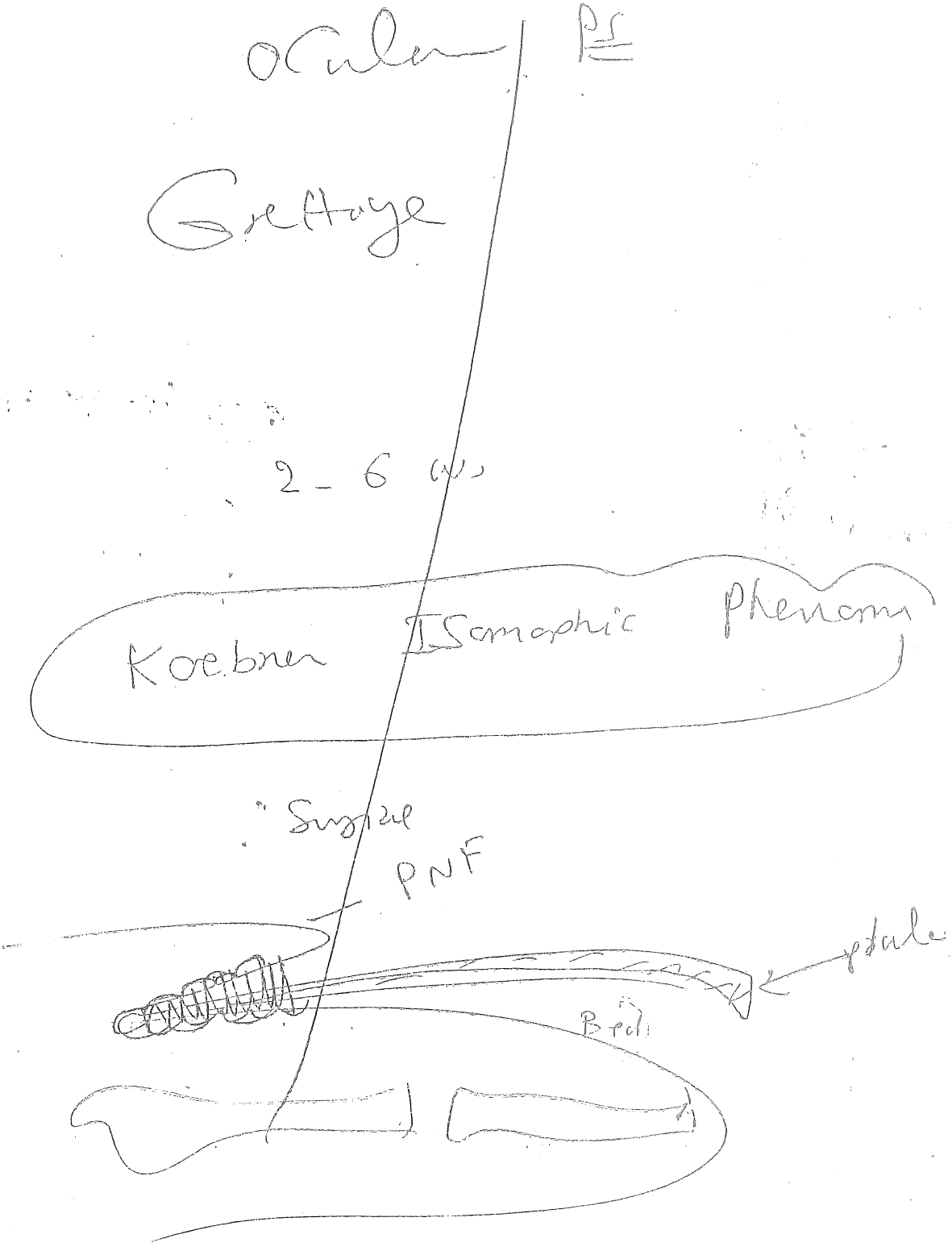
. 25-50%

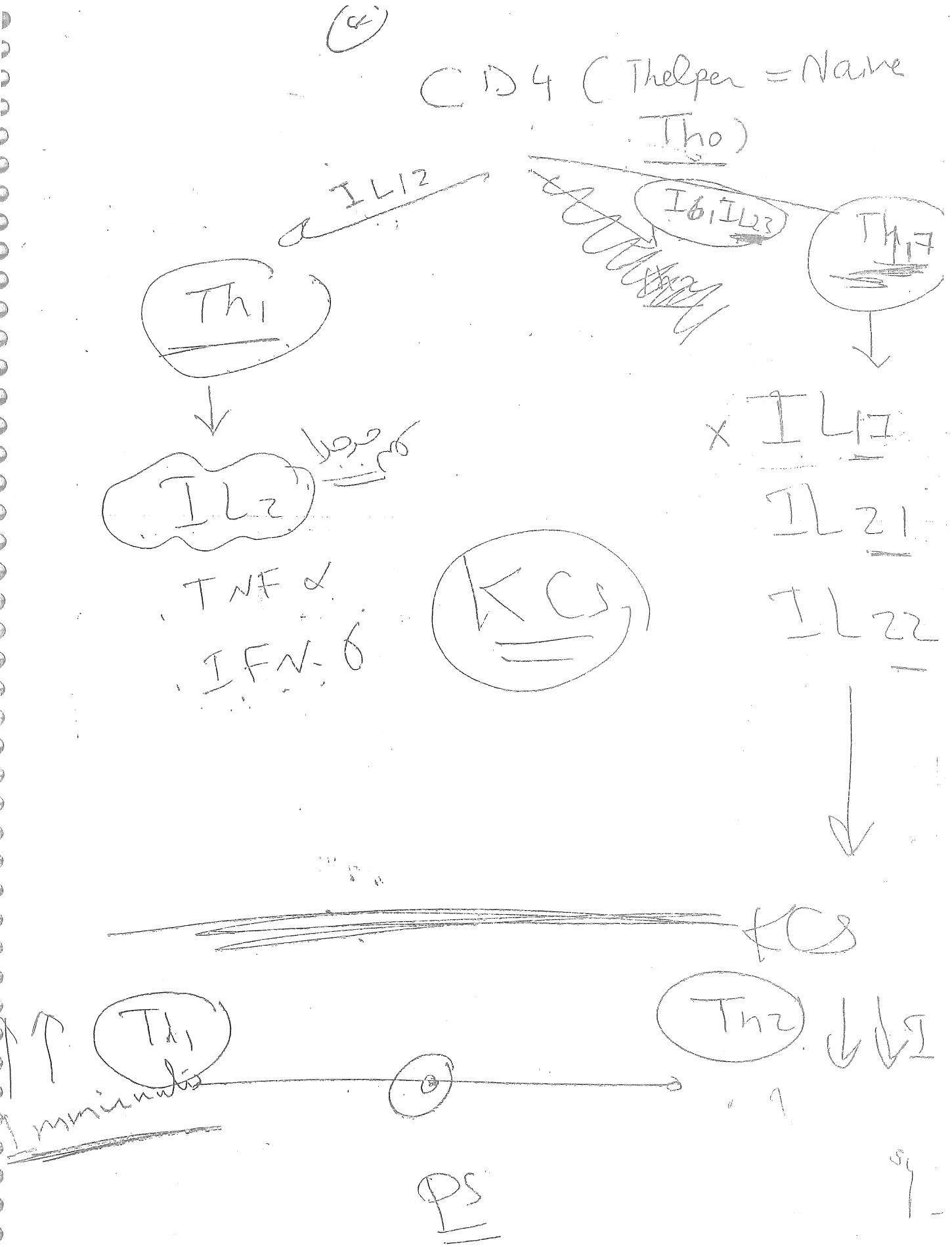
. 50-75% P1


C
LCs

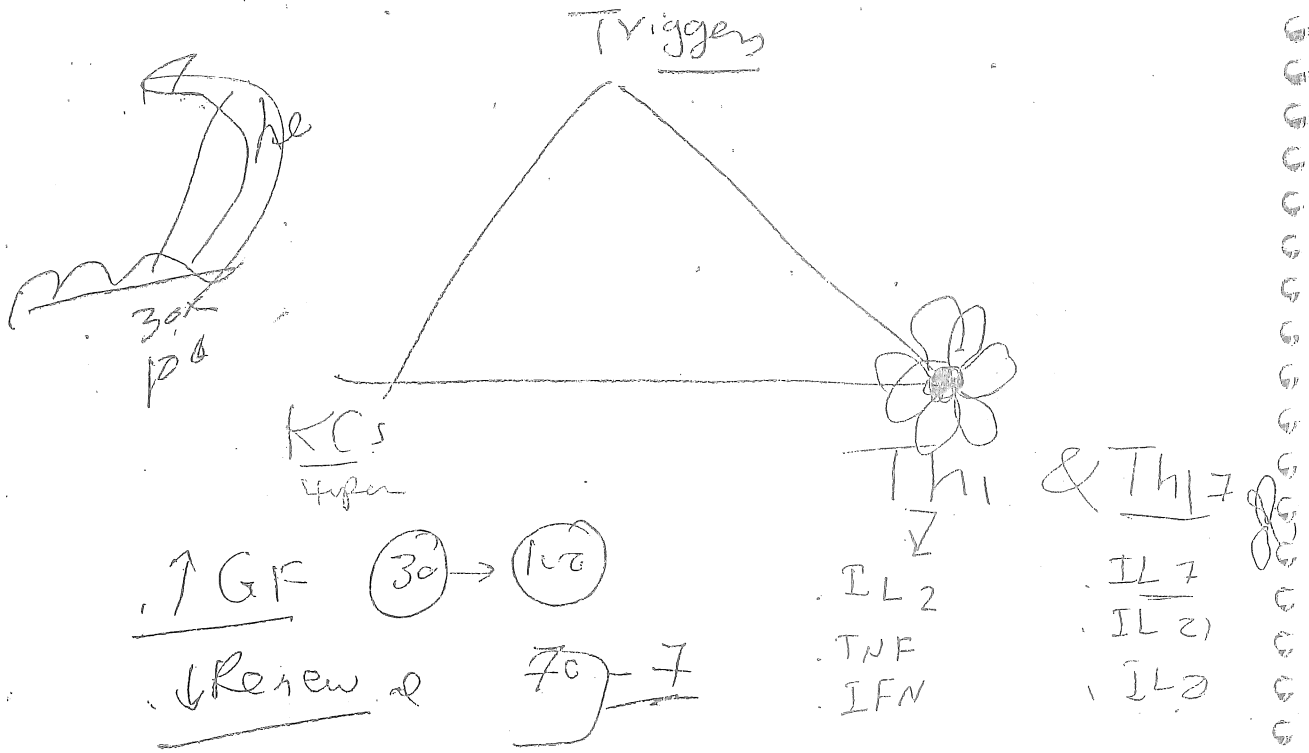

CD4 (Naive)
X
MHC-II
Major histocompatability
LCs
MHC II
LFA-1
ICAM-1
Naive
CD4
TCR
MHC II
CD2
LFA-3
CD28
B7

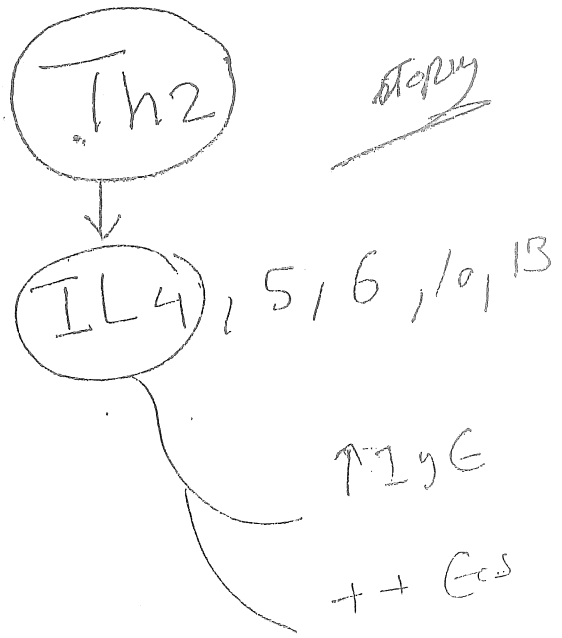
SKi.

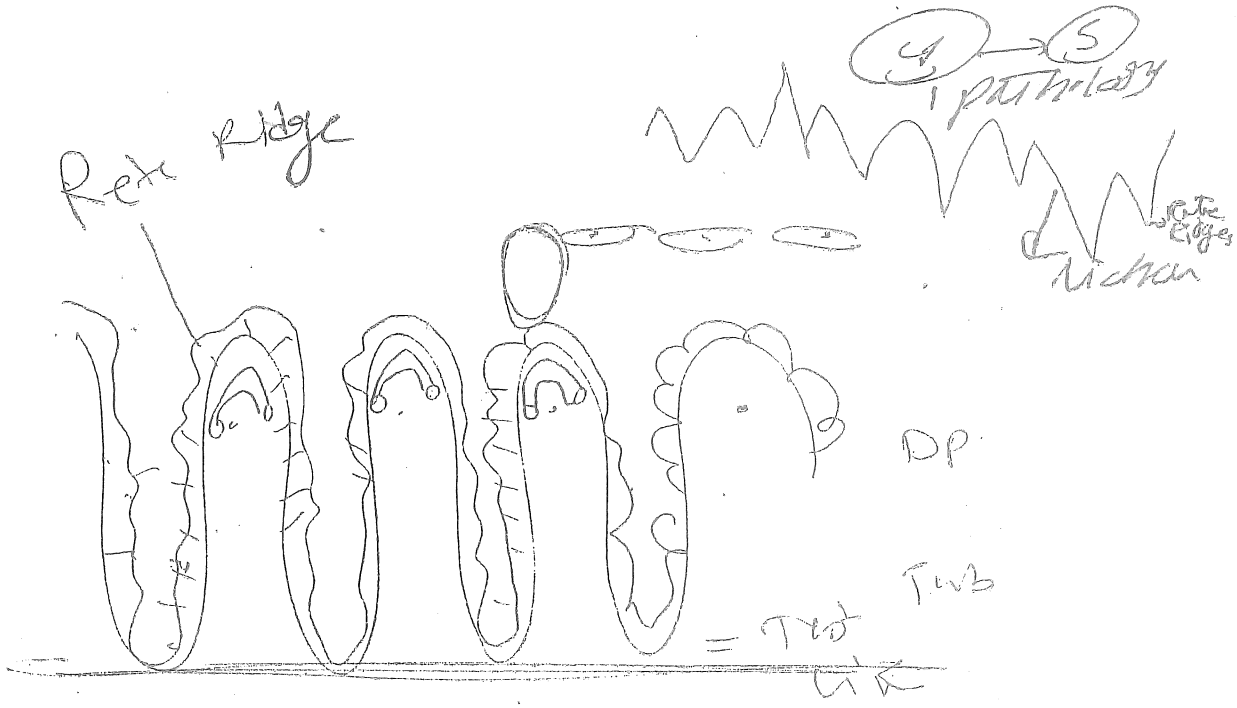


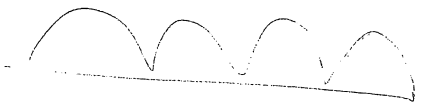

CD4 (Thelper = Naive
Th0)
IL12
IL6, IL23
Th17
Th1
IL2
TNF α
IFN-γ
IL17
IL21
IL22
KCs
KCs
Th2
Th1
IL1

PS


Triggers
KCs
Th1 & Th17
↑ GF
↓ Renew
IL 2
TNF
IFN
IL 7
IL 21
IL 2

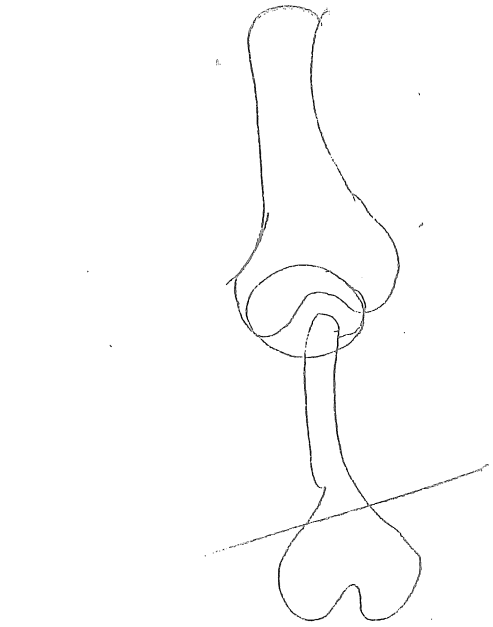

Th2
IL 4, 5, 6, 10, 13
++ Eos





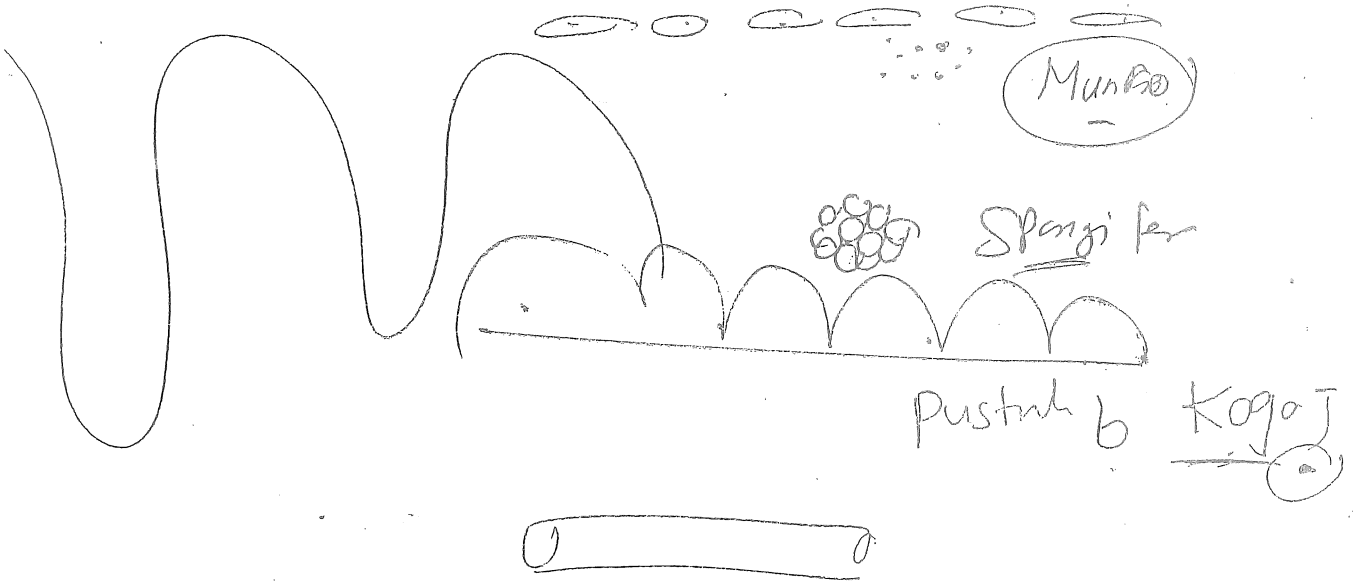
Pitting

- (1) Parakeratosis : Rel Nucl
- (2) Acanthosis : ↑ Thickness esp. Spicul Spinous cell Layer
- (3) Hypogranulosis
- (4) Regular elongated Rete Ridges.
- (5) D-P



pustular

ps



Date / /

Subject الموضوع Psoriasis التاريخ / /

(1) surface area.

(2) PASI score عن طريق oral.

acc to surface area → 2 to 10% palms → mild

byt it causes distress → so it considered severe psoriasis

in
- face
- palms
- genitalia

(3) location. (4) Ps. arthritis

(5) psychological impacts (6) financial.

++

15-20 L.E. (1) methotrexate (2) Acitretin

(3) cyclosporine (4) Biological

* methotrexate → 20 LE /month

folate (vit B complex - vit B_9) → Dihydrofolate → tetrahydrofolate

thymidilate ← Purine

DNA & RNA synthesis

- Dihydrofolate reductase ← enzymatic step
- Dihydroorotate synthetase
- thymidilate synthetase

Date / / التاريخ / /
Subject methotrexate acts on:- الموضوع

→ malignant cells
→ lymphoid cells
→ BM cells
→ hyperproliferative Ks

① competitive inh. of Dihydrofolate reductase enz.
② - inhibition of Ks proliferation
- immunosuppressive → rather than → Anti proliferative
lymphoid cells (خلايا) → 1000 times → Ks

③ Anti inflammatory
④ ↓ adenosine

thymidilate synthetase inhibited by methotrexate.
partial & reversible

oral (2.5 mg/tab)
IV, IM, SC
recently subcut.

oral: total dose 15-25 mg/week (0.2-0.4 mg/kg/w.)
by triple week schedule

IM → single dose
powder مسحوق
2cm → 50mg → vial
5cm

I give vial → when GIT upset occur
→ when I reach only 20mg & no response
dermatogenic → malabsorption

مع زيادة comp. ↑ → Erythrodermic
Exfoliative ps.

NB * methotrexate is hepatotoxic
& metabolized by kidney (3)

Date / / التاريخ

Subject الموضوع

injection → Pre-tt investigation → CBC
لو عندها → liver → hepatotoxic → HCV, B
→ renal → excreted by kidney
SGPT, SGOT / alkaline phos, Bilic

→ pregn.
→ chest: X-Ray
→ HIV

we can give it to renal failure by adjust dose

* test dose → vial → 5mg → IM → 1 week → stop MTX & dep. ← pancytopenia ← if repeat inv.

if → Normal → every w add 2.5mg
acc. to efficacy & SE
inv. every 2w.

SE لو ظهرت بالتدريج
لو ظهرت → leave him at this dose for 1-2 months
then withdraw 2.5 /w.

25 mg → change drug.

target of improvement → 4-6 weeks, maximum → 3 months

* indication in dermatology → FDA → Ps. → severe psy
Non FDA →

✓	✓	✓	Palm
✓	✓	!	Arm
✓	!	!	Palm

- CBC → anemia → ↓ Hb
severe impairment ✗
- liver → severe impa
active HCV
- renal impairment (↓ creatine clearance)
- pregnancy & Lactation (CI)
↳ 3-6 months after preg.

mrk → 3m.
dmrk → 3-6m

Date / /
Subject

التاريخ / /
الموضوع

male → ... → for 3m. after stopping

obese → ... patient ... mrk

TB → ... → reactivation.

GIT (subjective)
→ lung → pneumonitis, dyspnea
→ allergy → hypersensitivity, urticaria, angioedema
→ pregn. → teratogenicity, abortion
→ lactation → immunosupp. + malignancy
→ toxicity → pancytopenia
Idiosyncrasy → GIT upset
→ pneumonitis, dyspnea
→ not ... prophylaxis → recurrence
→ opp. infection

*Liver biopsy → low risk
→ 3-4gm cumulative dose
obese, DM, Alcohol → high risk → 1.5-2 gm
→ 1-1.5 gm

... تقييم ...
markers of fibrosis → ...
→ amino pro collagen 3
→ elastography
... تقييم ...

* staging & biopsy *
(1) no changes
(2) fatty liver, portal tract inf.
(3) → A → mild fibrosis
B → moderate or severe
(4) cirrhosis

1-2 → ...
3A → ... متوسط
3B → ...
4 → ... متقدم

Date / /

Subject

التاريخ / /

الموضوع

* Interactions :-

- Dapsone
- sulphonamides

inhi → Dihydrofolate synthetase → more toxicity

trimethoprim (septrin) THP.

↓ toxicity → folinic acid (leucovorin) 10 mg → tetrahydrofolate → purine

↓ thymidine

* folic a. → ↓

5mg → ↓ tab / day

excreted by kidney ← Acitretin → 10 mg, 25 mg

po in pregnancy ↑ cr 2 yrs → in europe, 3 yrs → USA

DISH → Diffuse idiopathic skeletal hyperostosis

X-Ray

↓ ↑ of choice in psoriatic ↓

Isotretinoin in ↓ of ps. → ↓ efficacy

MOA → ↓ cyclosporine

Ca++ calmodulin → CDK → IL2 → lymphocyte proliferation

stim. prod. of → Calcineurin → stim. production of IL2

Date / / التاريخ / /
Subject الموضوع

cyclo → cyclophinin Rs ← calcineurin prot

immune suppression ← IL2 & IL2 Rs level

calcineurin inhibitors

as → topical, systemic

(pimecrolimus

Rs. يشتغلوا بنفس الـ mechanism بتاع الـ cyclosporine

cyclosporine ← Rs بتاع الـ mechanism

very rapid onset of action

(category C

major life events → حدث مهم في حياة المريض

cyclosporine → nephrotoxic

(metabolized by liver

Biologics than cyclosporine ← أحسن من الـ

No cyclosporine ≠ Photherapy

→ nephrotoxicity

→ coronary artery

→ HTN

→ hypertrichosis

→ hyperplasia ← gums

→ hyperkalemia (no aldactone)

→ hyperlipidemia

→ hyperuricemia → gout

→ hypomagnesimia

Date / /

Subject

التاريخ / /

الموضوع

*interaction →

drugs inhibit [CYP450 enzyme] → Digitalis

→ erythromycin

→ Doxy

grapefruit → A-cok

~~grapefruit~~ → warfarin

→ Anti hyperlipidemic

→ viagra

stim. CPuso → rifampicin → digitalis → ...

digitalis ... → ~~A-cok~~

cyclosp: ← inducer CPuso ...

... ← diagram ...

*Dox ... ...

phase 1 → 1 month

Transition → 1 month

[photo therapy] ... BUVB → minimal SE

... in psoriasis

[Topical]

start

...

permovate

Betnovate

face, flexures → week potent ...

for Elidel.

vit D_3 → calcipotriol ...

Daivobet → calcipotriol + Betamethasone

maintance → for 1 year

HEGAZY NOTEBOOK

Date / /
Subject

التاريخ
الموضوع

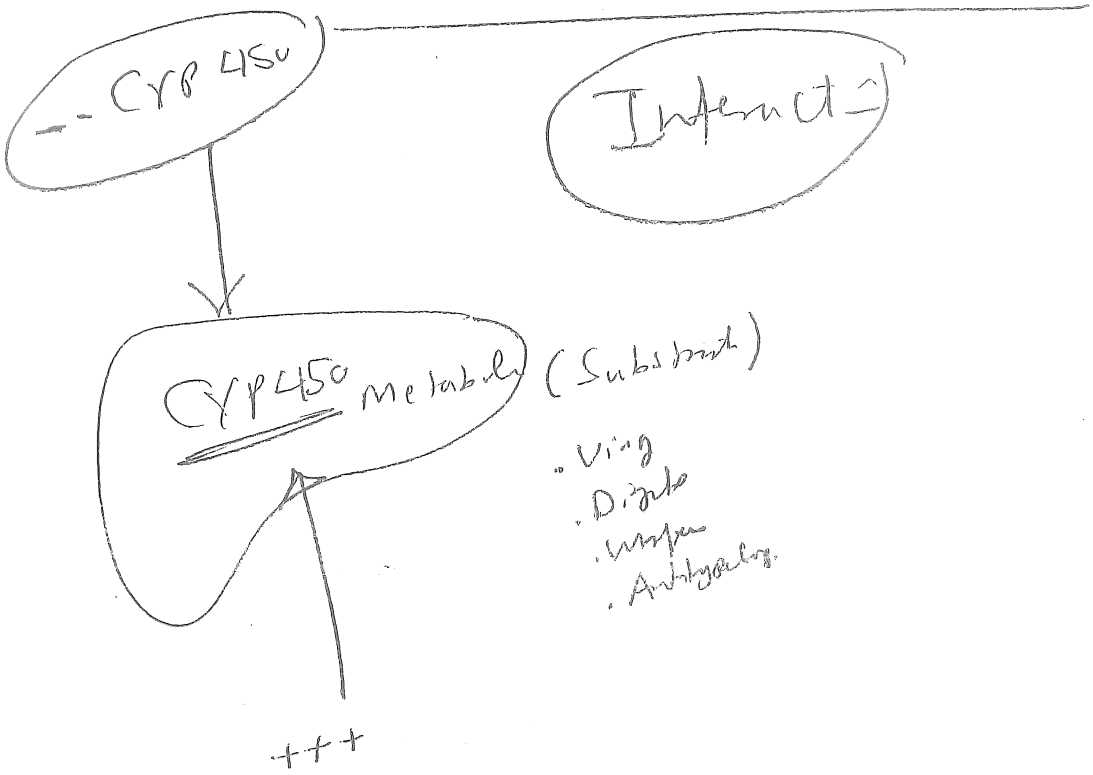
Triaphizole (Anti-androgenic)

scalp Dryness
dandruff

Betnovate / lotion

S.E

1. Nephrotoxicity
2. Carcinogenicity
3. Hypo
   - TNF
   - Hypochloremia
   - plasma Glu.
   - Kalemia
   - Lipidemia.
   - Uremia
4. Hypo Mg



(13)

Indwl

- EDA → PS → Rx Cad Ct / IH Resm. disablm / Major life event
  → AD
- NonFDA

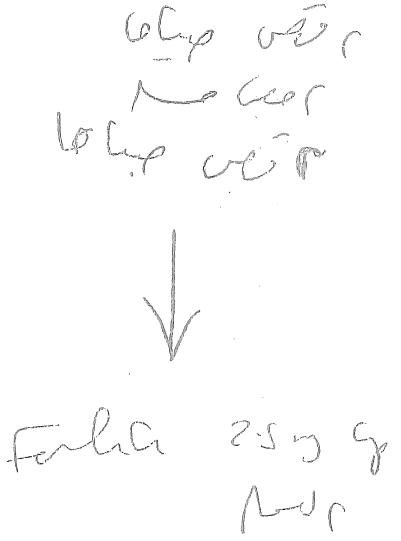
C.I & Cyd.

- Renal Nephrotoxic
- HTN :
- Liver Metabolized
- Pyo
- lactat
- Phototh.
- Mg.
- Active Eq.
- Malb.
- Inter.

12

- MTX
- folic acid

MTX



Folic 2.5 mg

Acitetin

Retinoid =

1. Antipsoriatic
2. ↑ KC diff
3. Antiflam

dose 0.5 - 1 mg/kg/d.

10 - 25 mg/d → D

11

Stage Biopsy

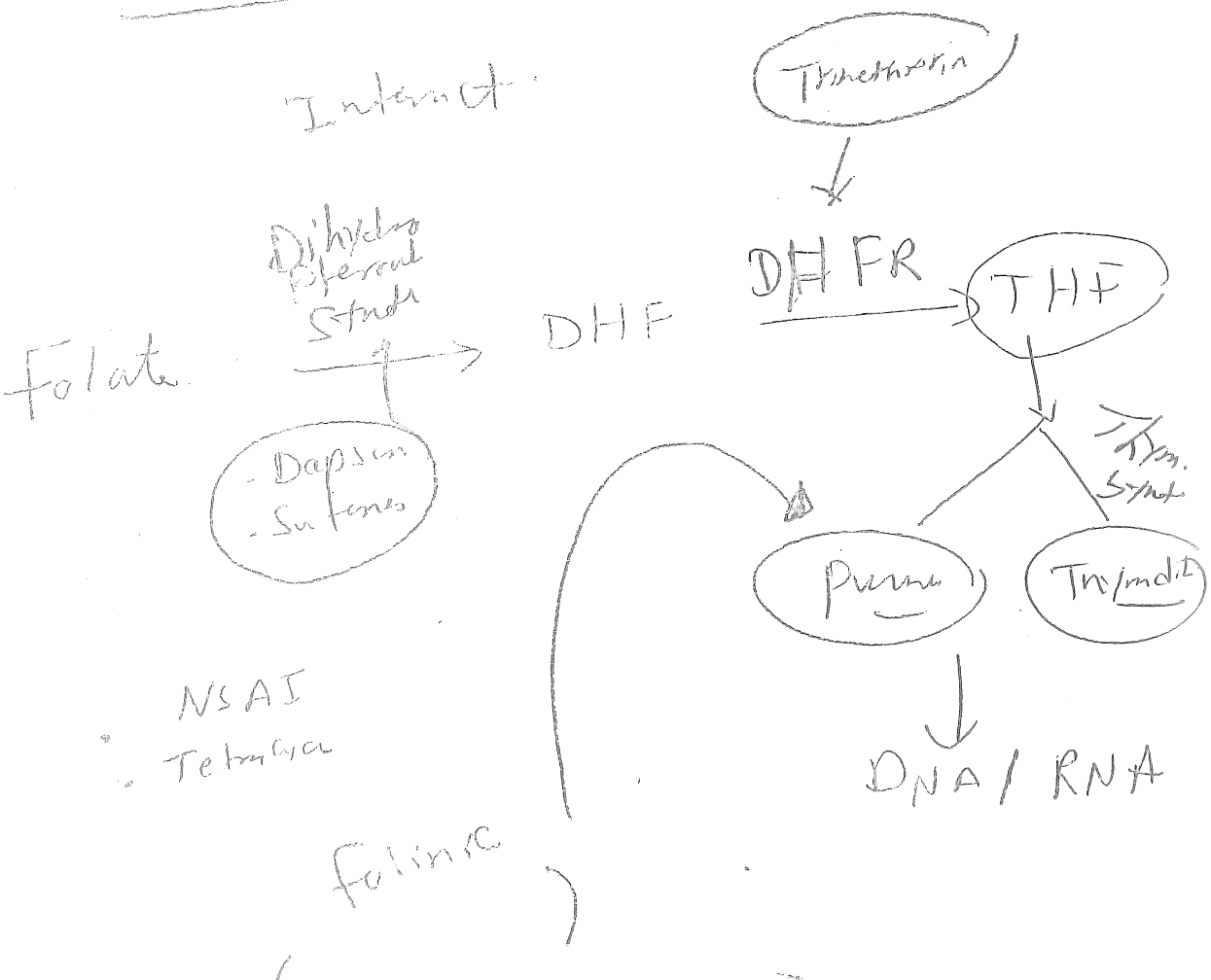
MTX

I → N: Etc } BMTX

II → Fatty, Portal infl.

III → (A) mild. (B) med Severe. } X

IV Cirrh.



9

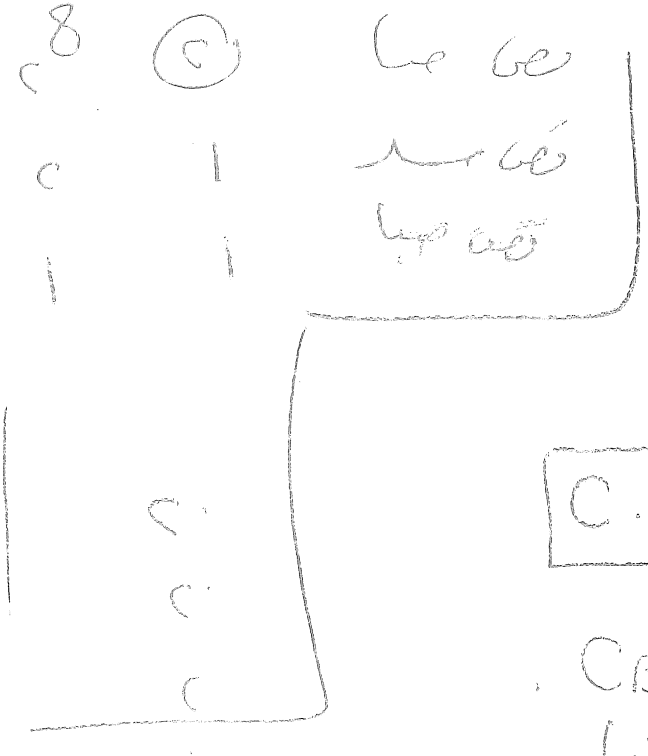
S.E

1. Subjective
2. CBC:
3. Liver:
4. Lung:
5. Skin
6. Preg & Lact
7. Idiosyn
8. MTX

Biopsy

- Low Risk
  - 3-4 gm
- High Risk
  - 1.5-2
  - 1-1.5

- Amino terminal procollagen III
- Elastography



C.I

- CBC Sever Imp
- Live : Active Hepa
- Renal :
- Prg & lact
  - ♀ 3-6 m.
  - ♂ 3 MT

RISKY

- Drug
- Alcm
- obese
- Cardiac Arrest
  - Hx of Post
  - Hx of fatal Lue

- Imm
- Infect
- Active PU

MT is Competitive Inh of

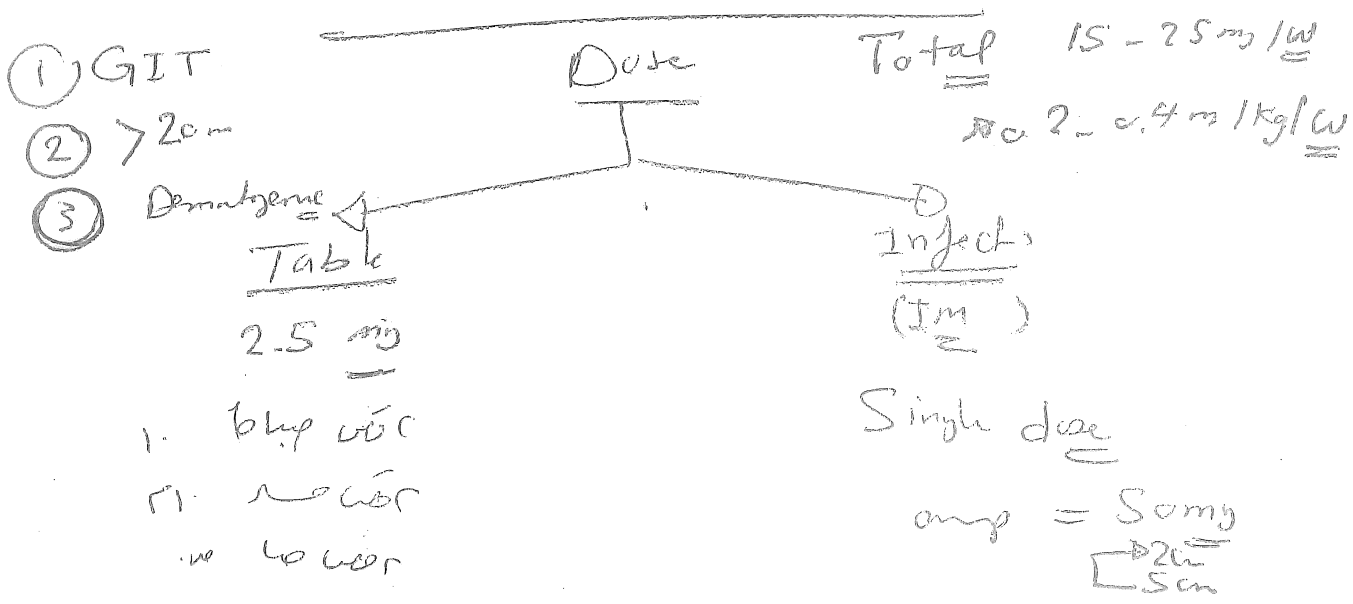
DHFR

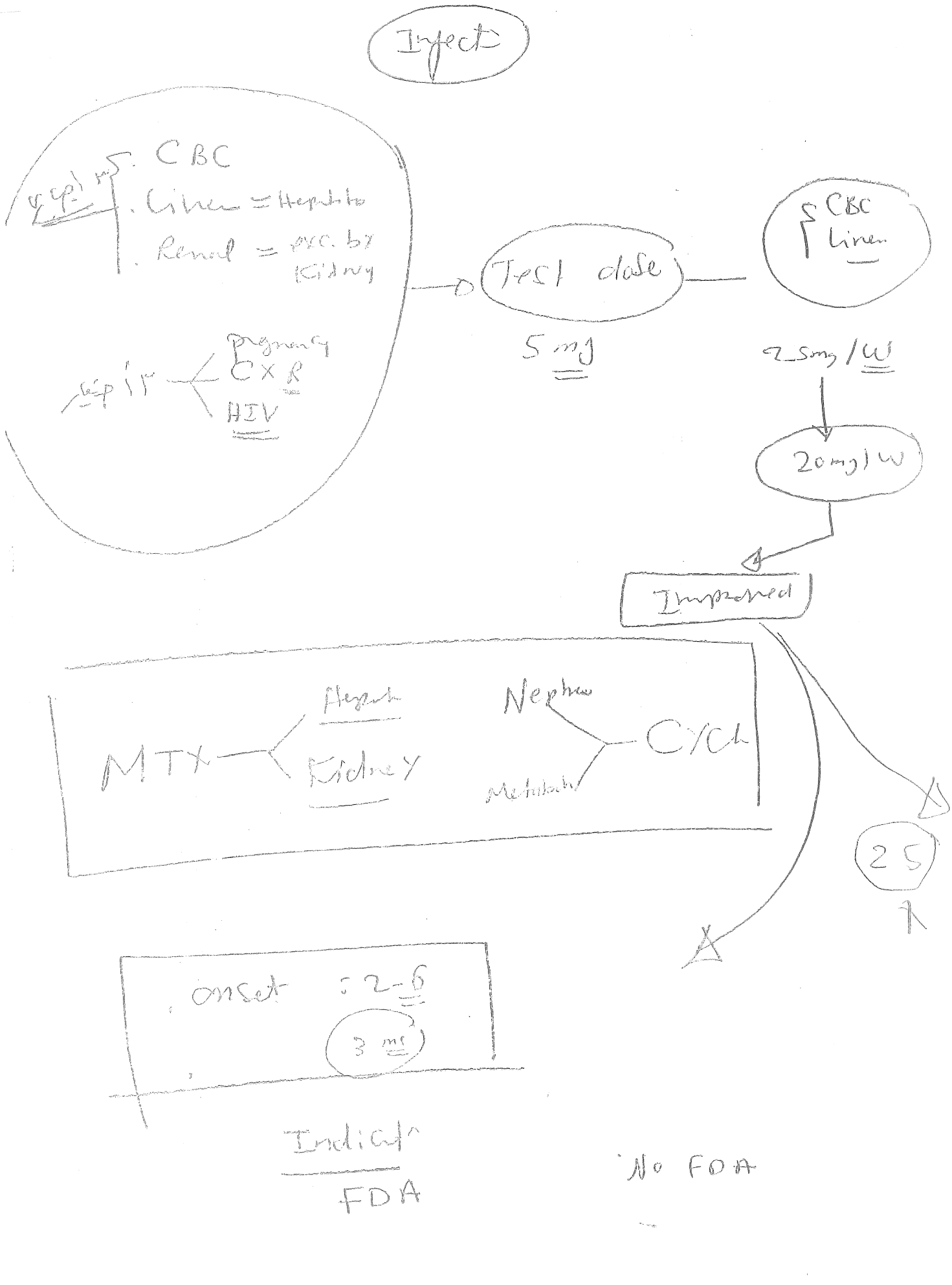
① -- KC Hypersensitivity (Anaphylaxis)

② Immunosuppression: Lymphocyte > Leucocytes

③ Antifolate, SAM

Thymidylate Synthase for MTX




Inject
CBC
Liver = Hepatic
Renal = exc. by Kidney
Pregnancy
CXR
HIV
Test dose
5 mg
CBC
Liver
2.5mg/W
20mg/W
Improved
MTX
Hepatic
Kidney
Nephro
Metabolic
C/Ch
25
onset : 2-6
3 ms
Indic^
FDA
No FDA

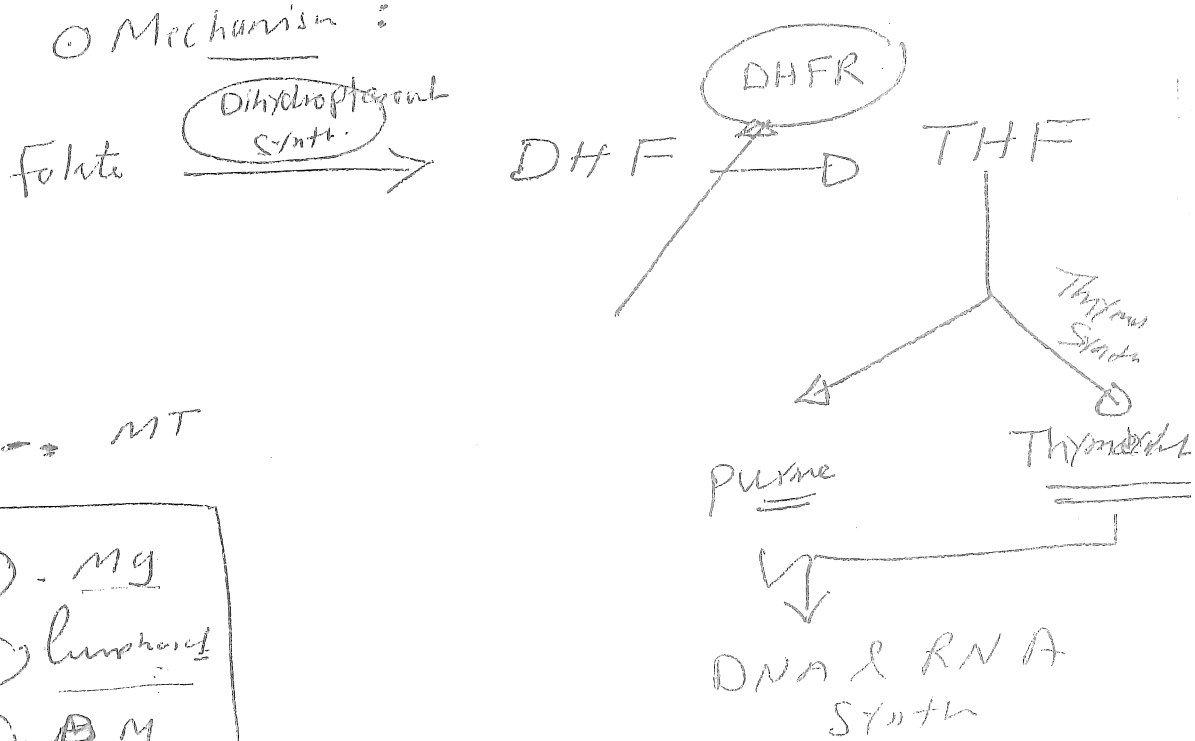
Systemic HT

- MTX
- Acebutolol
- Cycl.
- Biological

MTX

↓

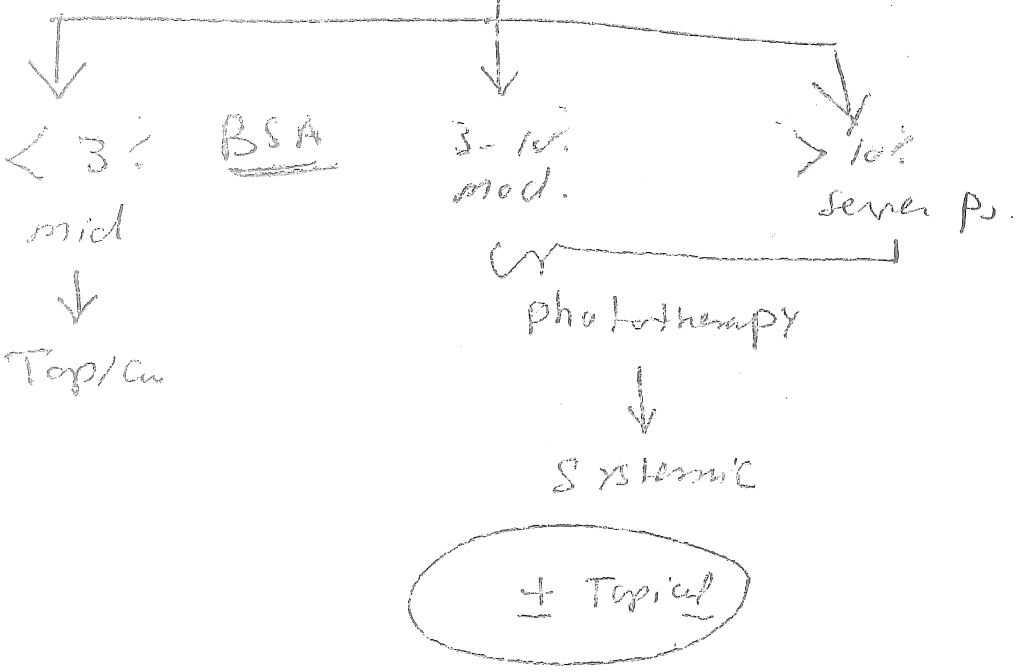
⊙ Mechanism :



→ MT

1. Mg
2. Lymphoid
3. BM
4. KC.

Severity Pt



??

Severity

(1). BSA

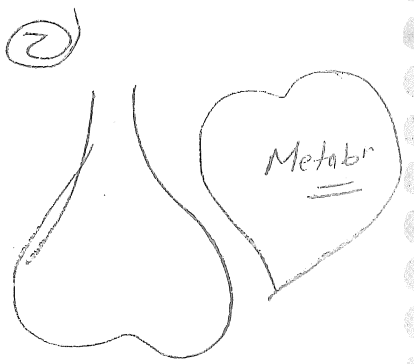
(2). PASI

		Head & Neck	upper Limbs	Trunk	lower Limbs
0-4	Erythema	1	2	4	3
0-4	Induration	0	1	0	1
0-4	Scaling	3	0	3	2
	Surface area 0-6	1	3	5	6

7-2

0
1 < 10%
2 10-30
3 30-50 4 50-70, 5 70-90 6 90-100

Treatment of Ps.



A. General Measures: Comorbidities

Obesity = Metab II

B. Topicals

C. photo th.

D. Systemic Ht.

E. Other

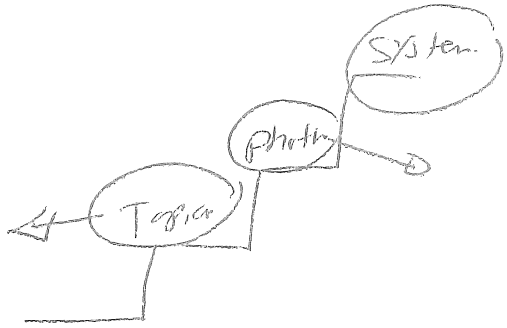
TC

- Smoking
- Drug :
  - Antimalind
  - NSAIDs.
  - BB
  - كمنع نافذ
- Stress :
- Trauma

~~Corneal~~ ~~Conjunctivitis~~

1) Topical

2) ~~Systemic~~



3) ph

Criteria

(1) . Central obesity
- Waist Cr.Cm ≥ 102cm ♂
- ≥ 88 Cm ♀

(2) . ↑ TGs ≥ 150 mg/dl

(3) . HDL . < 50 ♀
. < 40 ♂

(4) . BP ≥ 130/85

(5) . FBG ≥ 110 mg/dl

≥ 3 → Metabolic

Comodic

Systen

1. ocular manifest. Trichm.
2. PS. Arthritis
3. Nail
4. Crohn & UC
5. Psychological
. Depress.
. Succinyl
6. Metabolic Cholinest

Vit D analogues

CalCip

① Mech (3)

- ↓ K6&16
- ↑ K1, 2, 10
- ↓ IL8

②

③

S.E

① Irritation

② Inactivate

③ Calcipot phoo

CaCip

C.I

- preg
- lact
- HyperaCa
- Renal dysf
- Abn Bone Mtbm
- > 100 gm/d

- Topical Rt. < mild / mod. seve

1. CS
2. Vit. D
3. Tazarotene
4. Tar
5. Anthralin
6. SA

- Antipruritic
  ↑↑ KC intake
- Antistaphylococcal

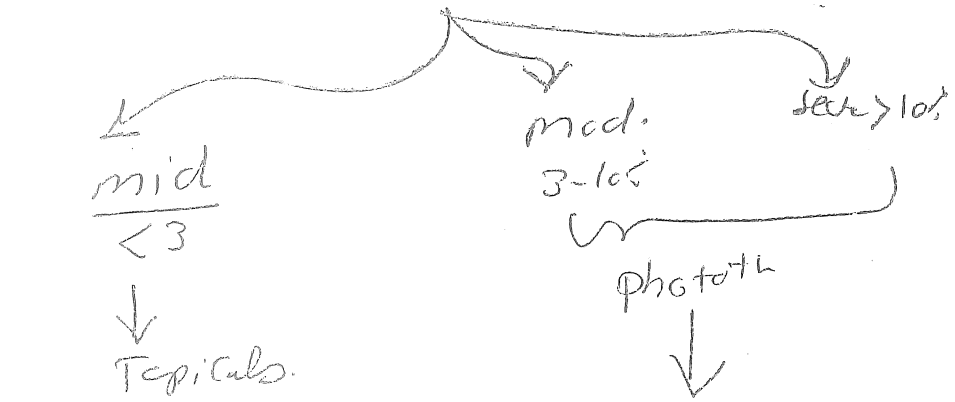
>3 Tachyphylaxis

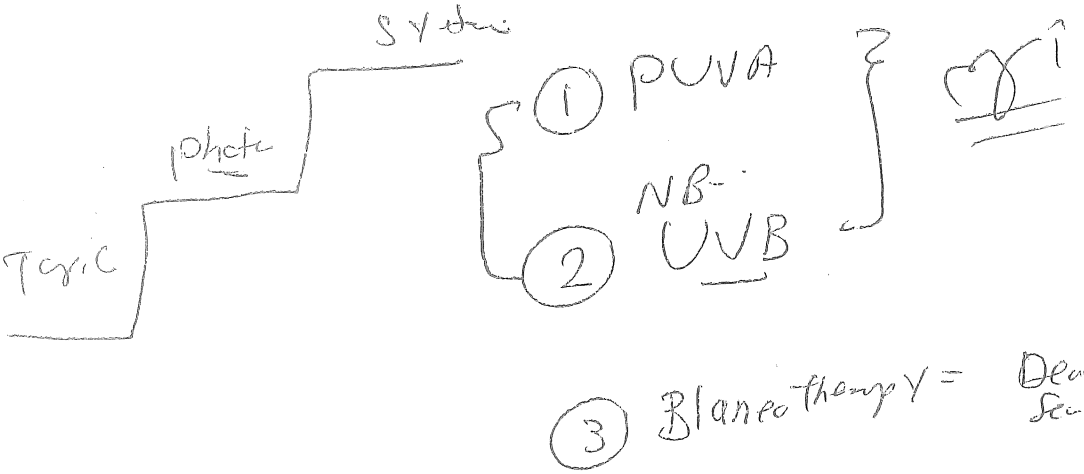
1. Clinic phase

2. Maint ph

weekend ph

Phototh





③ Balneotherapy = Dead Sea th

① Antipruf

② Anthralin Imm

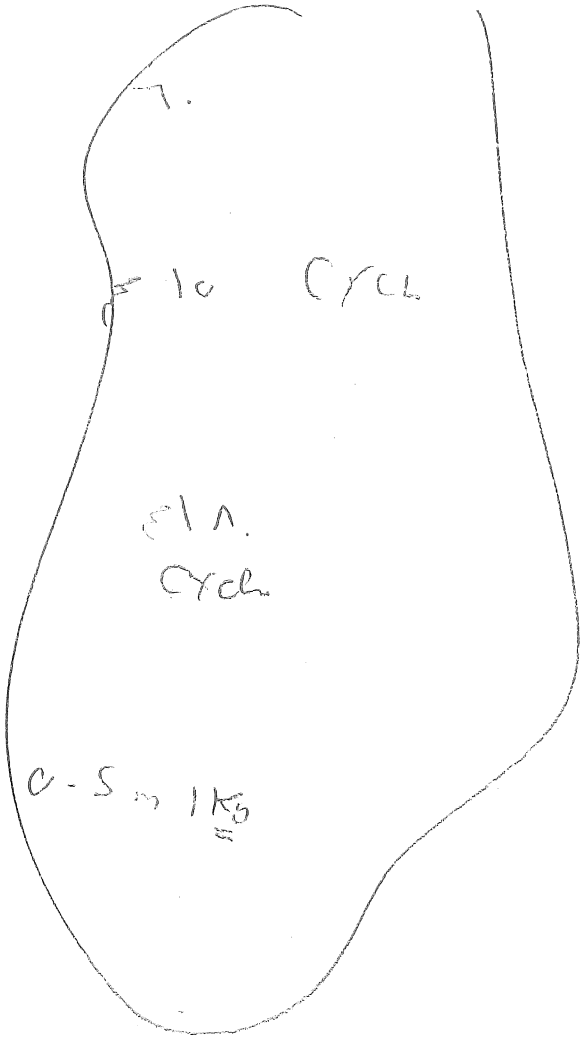
③ Bland. th

④ Heliosth

Salt

- Alone 2.5 m 1 Kg — 5 m
- Seq. the
- Combinat =

0.5 m 1 Kg



Sequential

(1) Cleaning

Cycl Alone

(2) Transmit

↓ Cycl

Acke

(3) Maintenance

Cl loss →

Acut & Repwn

Prett & dum HH In

- CBC : lenke
- Liver
- Renal
- Lipid profile — Hyper
- pregnancy test : C.I (X)

For 2 yr (Eur) & 3 yr (USA)

= DISH

- XRay

Alone : (Psoriasis)

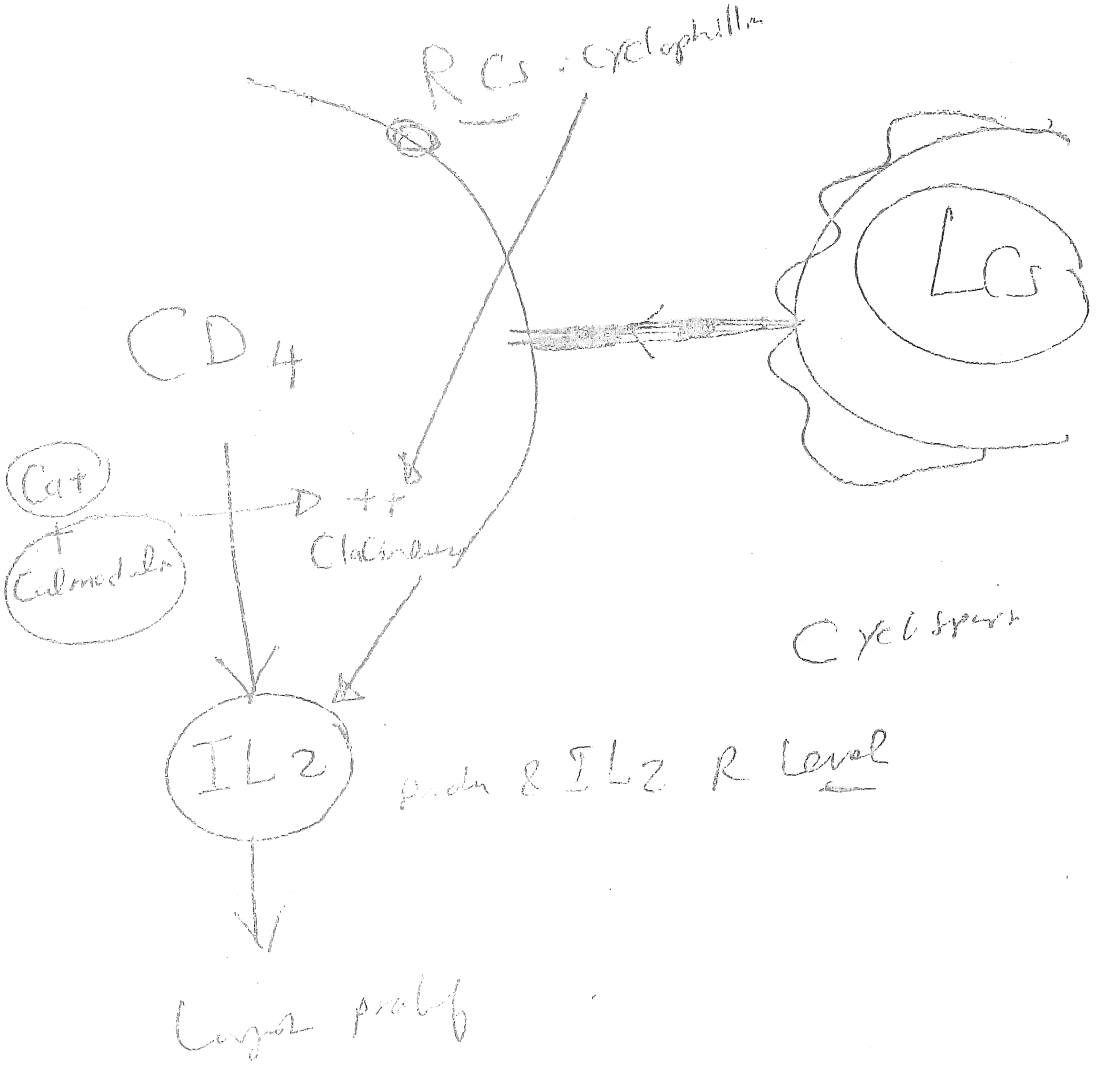
(Re) PUVA (Re) UVB

1. Traffic
2. ↓ dose
3. Ageing & Cancer

Isotretinoin

Cyclosporine = Ciclosporin

fungus →



Cyclospr : Calcineurin Inhibitn →
↓ IL2 & IL2 Rs (one →
↓ Imm

CsI